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Representing the North American Dyes Industry

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December 21, 2005

RETURN RECEIPT REQUESTED, PLEASE, BY E-MAIL

Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

ATTN: Chemical Right-to-Know Program
RE: HPV Registration No.

Dear Mr. Johnson:

ETAD North America's Stilbene Fluorescent Brighteners consortium, to fulfill its voluntary commitment as a chemical sponsor in the EPA's HPV Challenge Program, submits with this letter the test plan and robust summaries for the category of **stilbene fluorescent brighteners intermediates.**

As documented in my letter to you on November 10, 2005, ETAD North America revised its commitment by separating the category into a category for **stilbene fluorescent brighteners** and a category for **stilbene fluorescent brighteners intermediates.** The submission enclosed with this letter is for the intermediates only. The category of stilbene fluorescent brighteners was submitted today by separate transmission.

The members of the stilbene fluorescent brightener intermediates category are listed below. Included with this submission are the test plan, category justification, and robust summaries for the category members. Also included are supporting data for a surrogate chemical, CAS 78447-91-3.

Stilbene Fluorescent Brightener Intermediates

CAS No.	NAME
81-11-8	2,2'-Stilbenedisulfonic acid, 4,4'-diamino-
7336-20-1	2,2'-Stilbenedisulfonic acid, 4,4'-diamino-, disodium salt
3709-43-1	2,2'-Stilbenedisulfonic acid, 4,4'-dinitro-, disodium salt

For your convenience, we provide the test plan, category justification, robust summaries, and supporting data on a CD-ROM disk, which we are mailing today. The size of those documents precludes attaching them electronically.

Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers
1850 M Street, N.W., Suite 700 • Washington, D.C. 20036 • (202) 721-4100 • Fax (202) 296-8120 • www.etad.com

The participating companies in the ETAD North America Stilbene Fluorescent Brighteners consortium are Ciba Specialty Chemicals, Clariant, and Lanxess.

Please direct any questions, comments, or requests for additional information to me at 202-721-4154 or by e-mail at helmest@socma.com.

Sincerely,

C. Tucker Helmes, Ph.D.
Executive Director
ETAD North America

Enclosures

CD-ROM

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STILBENE INTERMEDIATES CATEGORY

HPV Challenge Program

TEST PLAN AND CATEGORY JUSTIFICATION

Submitted to the U.S. Environmental Protection Agency
Under the High Production Volume (HPV) Chemicals Challenge Program

By

The ETAD Fluorescent Whitening Agent Task Force

December 16, 2005

TABLE OF CONTENTS

1. Introduction

The Fluorescent Whitening Agent Task Force of ETAD has committed to sponsor a category of 3 intermediates for stilbene-based fluorescent whitening agents and dyes in the US EPA High Production Volume Chemical Program. The members of this Task Force are:

Ciba Corporation
Clariant Corporation
LANXESS Deutschland GmbH, successor of Bayer Chemicals AG and parts of Bayer AG

2. Identification of Category Members

The members of the Stilbene Intermediates Category are listed in Table 1. The molecular structures of category members are shown in Figure 1. The category consists of 3 sponsored stilbenes and one surrogate with supporting data. CAS Nos. 81-11-8 and 7336-20-1 are the same except that the former is the free sulfonic acid and the latter is the disodium salt. The surrogate (CAS No. 78447-91-3) has the same molecular structure as CAS No. 3709-43-1, except that CAS No. 3709-43-1 is the disodium salt, and CAS No. 78447-91-3 is the dipotassium salt.

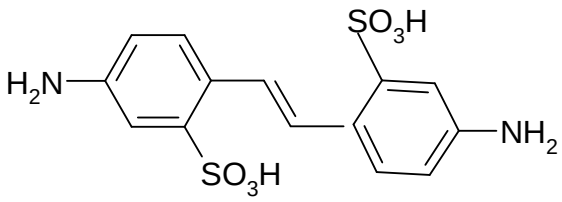
The members of the category (CAS Nos. 81-11-8, 7336-20-1 and 3709-43-1), plus the surrogate (CAS No. 78447-91-3) are intermediates that are used to manufacture fluorescent whitening agents and dyes.

Table 1. Identification of Category Members

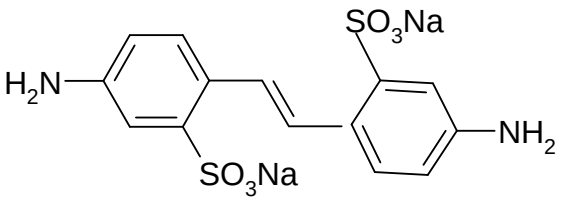
CAS No.	Chemical Name	Common or Trade Name
81-11-8*	4,4'-diaminostilbene-2,2'-disulphonic acid	Amsonic Acid
7336-20-1	disodium 4,4'-diaminostilbene-2,2'-disulphonate	
3709-43-1	disodium 4,4'-dinitrostilbene-2,2'-disulphonate	
78447-91-3	2,2'-Stilbendisulfonic acid-4,4'-dinitro, dipotassium salt	(surrogate for CAS No. 3709-43-1)

Bolded entries represent category members, non-bolded designate the surrogate with supporting data.
***** Reviewed at SIAM 4

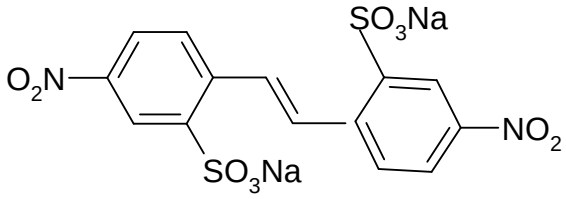
Figure 1. Chemical Structures of Category Members and Surrogates



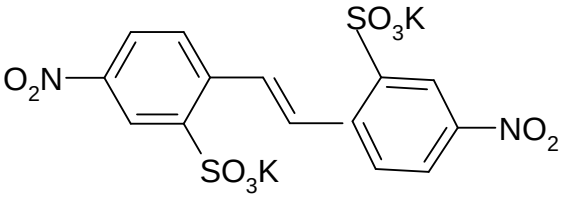
CAS No. 81-11-8



CAS No. 7336-20-1



CAS No. 3709-43-1



CAS No. 78447-91-3
(surrogate)

3. Justification for Stilbene Intermediates Category

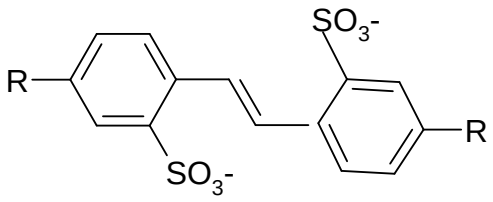
The merits for the category approach for the 3 sponsored chemical substances are summarized as follows:

- The substances possess similar chemical structures and functionality
- The substances display similar physical chemistry and environmental fate properties
- Existing data for the substances indicate that they exert similar effects with respect to aquatic and mammalian toxicology
- The use, release and exposure profiles for the substances are similar

The attributes summarized above are discussed in more detail below:

a. Category members possess similar molecular structures and functionality.

The three members of the category and the surrogate 78447-91-3 all possess the following stilbene backbone molecular structure, shown below:



for CAS Nos. 81-11-8 and 7336-20-1, R = NH_2

for CAS Nos. 3709-43-1 and 78447-91-3, R = NO_2

All category members possess two sulfonate groups. The only difference between the category members is in the substitution at the para positions on the benzene rings designated by the "R Group." Two of the members possess amino (-NH_2) groups as the R groups, and the other category member and surrogate possess nitro (-NO_2) groups as the R groups. CAS Nos. 81-11-8 and 7336-20-1 are identical substances, (where the R group is an amino function). The former is the free base and the latter is the disodium salt. The surrogate (CAS No. 78447-91-3) has the same molecular structure as CAS No. 3709-43-1 (where in both cases the R is a nitro function), except that CAS No. 3709-43-1 is the disodium salt, and CAS No. 78447-91-3 is the dipotassium salt.

b. Category members display similar physical chemical and environmental fate properties.

Since category members are all metal-organic salts or an internal salt (in the case of CAS No. 81-11-8), they exhibit high melting points, do not boil without decomposing and do not exert vapor pressure, except vapor pressure attributed to volatile impurities or additives, such as water. In addition, category members possess low or negative partition coefficients and are stable to hydrolysis. As a result of the stilbene portion of the molecule, these stilbene intermediates have an UV absorption maximum between 340 to 360 nm in water, which makes them subject to photodegradation in the hydrosphere. Finally, category members biodegrade only slowly.

c. Existing data for the substances indicate that they exert similar effects with respect to aquatic and mammalian toxicology.

Available studies suggest that the category members are of low toxicity to fish, annelids and bacteria and are of low to moderate toxicity to aquatic invertebrates and algae. With respect to mammals, the category members are of low acute or repeated dose oral toxicity, are not mutagenic or clastogenic, and are not reproductive or developmental toxicants. They are generally not irritating or sensitizing to skin and are slightly to moderately irritating to eyes.

d. Category members possess similar use, release and exposure profiles.

As stated above, the category members are the intermediates used to manufacture fluorescent whitening agents and dyes. CAS Nos. 3709-43-1 and 78447-91-3 are intermediates used to manufacture CAS Nos. 81-11-8 and 7336-20-1 via catalytic reduction of the nitro groups to the amine groups. CAS Nos. 81-11-8 and 7336-20-1 are then chemically converted on to dyes and fluorescent brightening agents. According to the SIDS Initial Assessment Report (SIAR) for CAS No. 81-11-8, which was reviewed at SIAM 4 (with Japan as the country sponsor), this category member is used to manufacture pigments and fluorescent brighteners in closed systems in Japan.

The sponsors of this category are not aware of any uses of these category members other than as industrial intermediates. As industrial intermediates, these materials are in general manufactured and converted to dyes and brighteners using closed systems. CAS Nos. 81-11-8 and 7336-20-1 may be sold to other companies who convert these substances on to dyes and brighteners. Therefore, these are not site limited intermediates. Exposures to category members are largely limited to an industrial setting, and minimized by being manufactured and chemically converted to final products using closed systems. Some environmental releases may be possible, but have not been quantified. Spills of CAS Nos. 81-11-8 and 7335-20-1 could occur during transport from the manufacturing sites to companies where the substances are converted to dyes and brighteners.

Examples of fluorescent brighteners made from CAS No. 81-11-8 and 7335-20-1 are given in Appendix A of the test plan. The brighteners in Appendix A are being sponsored as a separate category designated the Fluorescent Whitening Agent Category.

4. Criteria for Determining Adequacy of Data

All available studies for CAS Nos. 81-11-8, 7336-20-1, 3709-43-1 and 78447-91-3 were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1997). Studies receiving a Klimisch rating of 1 or 2 were considered to be adequate. The dossier for CAS No. 81-11-8 that was presented at SIAM 4 is not up to current standards and is not included in this submission. A new dossier has been created which contains data from the dossier presented at SIAM 4 and new information that was not available at SIAM 4. Information obtained from the dossier presented at SIAM 4 is clearly marked.

5. Discussion of Available Test Information

The test plan matrix (as shown in Table 2 on the next page) was constructed after a careful evaluation of all existing data (see below). This matrix is arranged by study type (columns) and screening data endpoints (rows), and indicates if data are provided for each end point in the sets of robust summaries.

Table 2. Plan Matrix for Stilbene Intermediates Category

CAS No.	**81-11-8**	**7336-20-1**	**3709-43-1**	78447-91-3
ENDPOINT				
PHYSICAL CHEMISTRY				
Melting point	Y	Y	M, C	M (NR)
Boiling point	NA	NA	NA	NA
Vapor Pressure	Y	NA	NA	NA
Water Solubility	Y	Y	C	Y
Kow	Y	M	M	M (NR)
ENVIRONMENTAL FATE				
Photodegradation	NR	Y	NR	NR
Stability in Water	Y	S	S	S (NR)
Biodegradation	Y	Y	Y	Y
Transport between Environmental Compartments (Fugacity)	M	M	M	M (NR)
ECOTOXICITY				
Acute Toxicity to Fish	Y	Y	C	Y
Acute Toxicity to Aquatic Invertebrates	Y	Y	C	NR
Toxicity to Aquatic Plants	Y	Y	C	NR
Toxicity to Bacteria (NR)	Y	NR	NR	Y
Toxicity to Terrestrial Organisms (NR)	NR	NR	NR	NR
Chronic Toxicity to Fish (NR)	NR	NR	NR	NR
Chronic Toxicity to Invertebrates (NR)	Y	NR	NR	NR
TOXICOLOGICAL DATA				
Acute Toxicity	Y	Y	C	Y
Repeated Dose Toxicity	C	Y	C	NR
Genetic Toxicity-Mutation	Y	Y	C	Y
Genetic Toxicity-Chromosomal Aberrations	Y	Y	C	NR
Carcinogenicity (NR)	C	Y	C	NR
Toxicity to Reproduction	Y	C	C	NR
Developmental Toxicity	Y	C	C	NR
OTHER TOXICITY DATA				
Irritation (NR)	Y	Y	Y	Y
Sensitization (NR)	N	NR	NR	NR
Human Experience (NR)	Y	NR	NR	NR

Category members are depicted in boldface type. Y = endpoint filled by experimental data;
C = endpoint filled by category approach; NA = not applicable; S = endpoint filled by general analysis of chemical structure; M = endpoint filled by modeling; NR = not required

5.1 Physical Chemical Properties for Category members

The physical chemical properties for category members are summarized in Table 3.

Table 3. Chemical/Physical Property Data for Stilbene Intermediates Category

Chemical CAS No.	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (hPa) @ 20ºC	Water Sol. (g/l) @20ºC	Log Kow
81-11-8	> 300 [a]	No data	< 1.3 (25ºC) [b]	0.032 at 25 [b]	-1.7 [c]
7336-20-1	> 300 [d] 349.84 [f]	No data	No data	> 100 [e] (21ºC)	-3.99 [f]
3709-43-1	349.84 [f]	No data	No data	No data	-2.52 [f]
78447-91-3	> 200 [g] 349.84 [f]	No data	No data	4.34 [h]	0.2 [i] -2.52 [f]

Bolded type represents category members; regular type represents the surrogate with supporting data.
[a] Huang- Minlon, 1948; [b] MITI, 1994; [c] Bayer AG, 1991a, calculated; [d] Ciba Geigy AG, 1986; [e] Ciba Geigy AG, 2005; [f] estimated using EPIWIN; [g] Bayer AG , no year listed; cited in an IUCLID document for CAS No. 78447-91-3; [h] Bayer AG, 1989a; [i] Bayer AG, 1991b

5.1.1 Melting Point

Measured melting point data are available for two of the category members. Category members have consistently high melting points, as would be expected for organic molecules that exist primarily as ionic salts. The estimated melting points are generally consistent with the measured melting points.

5.1.2 Boiling Point

None of the category members will exhibit a boiling point range, because they are either organo sodium salts or an inner salt. Organic salts exist in ionic form instead of unionized molecular form and will decompose on heating to temperatures above the melting point without boiling. As shown in Table 3, melting of category members generally does not occur below 300°C (with the exception of CAS No. 78447-91-3, which begins to decompose above 200°C), and decomposition (not boiling) would then be expected above these temperatures.

5.1.3 Vapor Pressure

Since all category members exist as ionized organic salts, and therefore do not exist as molecules that can volatilize, vapor pressure determination is not relevant or needed. A measured vapor pressure of 1.3 hPa is reported for CAS Nos. 81-11-8, but it is likely that this appreciable vapor pressure is attributable to the presence of water or other volatile impurities. As salts, category members themselves will not exert appreciable vapor pressure. No testing is needed or planned.

5.1.4 Partition Coefficient

Partition coefficient data are available for all category members as shown in Table 3. The partition coefficients were estimated using EPIWIN Kowwin or a similar model. The values are low or negative (ranging from 0.2 to –3.99), which are consistent with the low Log Pows that would be anticipated for organic salts.

5.1.5 Water Solubility

Water solubility data are available for CAS Nos. 81-11-8, 7336-20-1 and 78447-91-3. The values range from < 1 g/l for the acid (CAS No. 81-11-8), to > 100 g/l for the corresponding salt (CAS No. 7336-20-1). The value for CAS No. 78447-91-3 (4.34 g/l) will be predictive of that for CAS No. 3709-43-1, since the former is the potassium salt and the latter is the sodium salt of the same molecule.

5.1.6 Summary/Test Plan for Physical Properties

Adequate measured information is available for physical properties. The high melting points are consistent with molecular structure and functionality (all category members are organic salts). As metal organic salts or inner salts, category members exist in ionic form and not as discrete molecules. Therefore, these materials do not boil without first undergoing decomposition at or above their melting points. Nor do they exert significant vapor pressure, other than that attributable to volatile impurities or additives that may be present, such as water. Sufficient estimated data are available for category members with respect to partition coefficient to predict

that Log Pow values will be low or negative (consistent with the presence of multiple sulfonic acid salt functions). The water solubility value for CAS No. 78447-91-3 is predictive of that for CAS No. 3709-43-1. No further testing is therefore planned for physical properties.

5.2 Environmental Fate Data for Category Members

5.2.1 Photodegradation

None of the category members volatilize to any degree, since they are all ionized organic salts. Therefore, they will not be found in any significant concentration in the atmosphere other than in particle form. For this reason, atmospheric photodegradation is not an appreciable or important degradative pathway, and testing for atmospheric photodegradation would not serve a useful purpose.

However, since the category members have the ability to absorb part of the terrestrial UV-sunlight (λ = 300 – 400 nm) and transform it into visible, blue fluorescence light (Kramer, 1996), they are potentially photodegradable substances. A half-life of 1.78 x 10^{-2} years and a rate constant of 6.19 x 10^{-11} mol/l/sec in water were estimated by MITI (1994) for CAS No. 81-11-8 (according to the method of Lyman et al. [1981]) for the direct photodegradation of the material in water due to the absorption of UV light. The available data indicate that stilbenes have a strong potential to undergo photodegradation in the hydrosphere.

5.2.2 Stability in Water (Hydrolysis)

CAS No. 81-11-8 has been found to be stable in water at pH 4, 7 and 9 in an OECD Guideline 111 study (MITI, 1994), which was reviewed at SIAM 4. The available measured data are consistent with predicted stability to hydrolysis based on molecular structure. The category members do not possess functional groups (esters, carbamates, etc.) that are normally expected to be susceptible to abiotic hydrolysis. Based on measured data and known lack of functionality susceptible to hydrolysis, sufficient information exists to address the hydrolysis endpoint.

5.2.3 Environmental Transport

Because the category members are salts, they cannot volatilize to the atmosphere, but would enter the atmosphere only in particulate form and in very limited amounts, where they would be removed by wet or dry deposition. The appreciable water solubilities of category members and their low or negative partition coefficients, suggest a limited potential to bioaccumulate, and a strong tendency to partition to the hydrosphere, as well as soil.

The EPIWIN Level III Fugacity program has been run for the category members using measured values for melting point water solubility, and partition coefficient (when available). As expected, the model results predict that the stilbene intermediates will partition predominately to water and soil and negligibly to the atmosphere and biota (Table 4).

Table 4. Level III Fugacity Modeling for Category Members

CAS No.	Fugacity Mass Percent				Half-lives (Hours)			
	Air %	Water %	Soil %	Biota %	Air	Water	Soil	Biota
81-11-8	0	57.8	42.1	0.107	1.18	900	900	3600
7336-20-1	0	57.9	42.0	0.107	1.18	900	900	3600
3709-43-1	0	59.1	40.8	0.112	1.47	1440	1440	5760

Emission rates inputted to the model are 1000 kg/hr to water and to soil, and 0 kg/hr to air

5.2.4 Biodegradation

As shown in Table 5 below, all studies that have been conducted on the category members indicate that most members are not readily biodegradable.

Table 5. Biodegradation Rates for Stilbene Intermediates Category

Category Member	**Biodegradation Rate**
81-11-8	5% after 28 days (OECD 302B) [a] 0% (BOD), 1-4% (HPLC), (OECD 301C) [b]
7336-20-1	< 15 % after 56 days (OECD 302B) [c]
3709-43-1	4.3% after 31 days [(OECD 2) A-12] [d]
78447-91-3	0.7% after 29 days (modified OECD Screening Test) [e]

Bolded type represents category members; regular type represents the surrogate with supporting data.
[a] Bayer AG, 1989b; [b] MITI (1994), reviewed at SIAM 4; [c] ETAD, 1992; [d] Ciba-Geigy, 1986;
[e] Ciba-Geigy, 1989a

5.2.5 Summary/Test Plan for Environmental Fate Parameters

Since the category members do not volatilize, atmospheric photodegradation is not an important degradative pathway, and conducting atmospheric photodegradation studies would not be useful. Available data indicate that these materials undergo photodegradation in the hydrosphere as well as slow biodegradation. Studies performed with all members of the category indicate that these materials are not readily biodegradable.

Level III fugacity modeling suggests that category members, when released to the environment, will partition predominately to soil and water, and negligibly to the atmosphere. Further environmental fate testing is not planned.

5.3 Aquatic Toxicity Data

Aquatic toxicity data for the category members are summarized in Table 6.

Table 6. Aquatic Toxicity of Stilbene Intermediates Category

Chemical	Fish Acute Toxicity LC_{50} (mg/l)[a]	Invertebrate Acute Toxicity EC_{50} (mg/l)[b]	Algae Acute Toxicity EC_{50} (mg/l)[c]
81-11-8	>1000 (1) 200 (LC0) (2)	130 (1) 210 (24 hr) (1)	76 (1)
7336-20-1	≥ 500 (3)	300 to 500 (4)	> 100 (3)
3709-43-1	> 1000 (5) [d]	No data	No data
78447-91-3	> 3395 (6)	No data	No data

Bolded type represents category members; regular type represents the surrogate with supporting data.
[a] 96 hours unless listed otherwise, [b] *Daphnia magna* (48 hrs) unless stated otherwise; [c] 96 hours unless stated otherwise; [d] Study given a reliability rating of 4 (not assignable due to insufficient documentation); (1) EA, 1994; (2) Bayer AG (date unknown); (3) ETAD, 1992; (4) Bayer AG, 1986; (5) Ciba-Geigy, 1986; (6) Fraunhofer-Institut, 1989

5.3.1 Acute Fish Toxicity

An OECD Test Guideline 203 study was conducted with CAS No. 81-11-8 in *Oryzias latipes* (Japanese Rice Fish) (EA, 1994). The 96-hour LC50 value was > 1000 mg/l (highest concentration tested). The 48-hour LC0 for CAS No. 81-11-8 in a non-GLP study with *Leuciscus idus* (golden orfe) was 200 mg/l. Both of these studies were included in the SIDS dossier accepted at SIAM 4.

OECD Test Guideline 203 studies conducted in *Brachydanio rerio* (zebrafish) indicate a 96-hour LC0 value of ≥ 500 mg/l for CAS No. 7336-20-1 (ETAD, 1992) and ≥ 3395 mg/l for a formulation containing 64.4% CAS No. 78447-91-3 (Fraunhofer-Institut, 1989). A study conducted in *Brachydanio rerio* that was given a reliability rating of 4 (not assignable) due to insufficient information indicates a 96-hour LC50 value of > 1000 mg/l for a formulation containing 60% CAS No. 3709-43-1 and 35% water (Ciba-Geigy, 1986).

5.3.2 Acute Toxicity to Aquatic Invertebrates

The 24-hour EC50 value for CAS No. 81-11-8 in an OECD Test Guideline 202 study conducted in *Daphnia magna* is 210 mg/l (EA, 1994), which was reviewed at SIAM 4. The 48-hour EC50 value for immobility, determined in the 21-day OECD Test Guideline 202 study described under 5.3.5 below, is 130 mg/l CAS No. 81-11-8 (EA, 1994). A 48-hour EC50 value between 300 and 500 mg/l was determined for CAS No. 7336-20-1 in an OECD Test Guideline 202 study in *Daphnia magna* (ETAD, 1992).

5.3.3 Acute Toxicity to Aquatic Plants

Results of an OECD Test Guideline 210 study reviewed at SIAM 4 indicate that the 72-hour EC50 value for CAS No. 81-11-8 in *Selenastrum capricornutum* is 76 mg/l (EA, 1994). An OECD Test Guideline 201 study listed a 72-hour EC50 value of > 100 mg/l CAS No. 7336-20-1 for either *Scenedesmus subspicatus, Selenastrum capricornutum* or *Ankistodesmus bibraianus* (actual species used was not listed) (ETAD, 1992).

5.3.4 Acute Toxicity to Bacteria

The 24-hour EC0 values reported by Bayer for CAS Nos. 81-11-8 at SIAM 4 and 7336-20-1 in *Pseudomonas fluorescens* bacteria are 1000 mg/l.

The 3-hour EC50 values for inhibition of respiration of activated sludge by CAS Nos. 7336-20-1 and 78447-91-3 are > 100 and > 10000 mg/l, respectively (Ciba-Geigy AG, 1986; Ciba-Geigy, 1989b).

5.3.5 Chronic Toxicity to Aquatic Species

The chronic toxicity of CAS No. 81-11-8 to *Daphnia magna* has been tested according to OECD Test Guideline 202. Forty daphnids were exposed in an open system to each of 5 nominal concentrations ranging from 21-210 mg/l. Immobility and reproduction rate were monitored for a period of 21 days. The 21 day EC50 value (with 95% confidence limits) for immobility was 44 mg/l (63-86 mg/l). The 21 day EC50 value (with 95% confidence limits) for reproduction was 92 mg/l (85-98 mg/l) (EA, 1994). This study was reviewed at SIAM 4.

5.3.6 Test Plan for Aquatic Toxicity

Adequate acute fish toxicity tests have been performed for all materials in the category. All 96 hr LC50 values are ≥ 500 mg/l. Invertebrate toxicity testing has been performed on all category members except CAS No. 3709-43-1. All EC50 values in *Daphnia magna* for the tested category members are > 100 mg/l. Algae toxicity tests that have been performed on CAS Nos. 81-11-8 and 7336-20-1 indicate LC50 values ≥ 76 mg/l. Additional studies indicate that the test materials are of low toxicity to bacteria. Based on similarities in structure, it is expected that the EC50 values for CAS No. 3709-43-1 for Daphnia and algae will be similar to those of CAS Nos. 81-11-8 and 7336-20-1. No additional testing is necessary.

5.4 Mammalian Toxicity

Acute mammalian toxicity studies that have been performed are summarized in Table 7.

Table 7. Acute Mammalian Toxicity of the Stilbene Intermediates Category

Chemical	Acute Rat Oral LD_{50} (mg/kg)	Acute Rat Inhalation LD_{50} (mg/l)	Acute Rat Dermal LD_{50} (mg/kg)
81-11-8	>3000 (LC0) (1) 47000 (guinea pig) (2)	No data	No data
7336-20-1	> 5000 (3)	No data	No data
3709-43-1	> 16000 (4)	No data	No data
78447-91-3	> 2000 (5)	No data	No data

Bolded type represents category members; regular type represents the surrogate with supporting data.
(1) Smith and Quinn (1992); (2) Zaitseva and Kulikov, 1980; (3) Loeser, 1979; (4) reference unknown. Data cited in an IUCLID document for CAS No. 3709-43-1. Assigned a reliability rating of 4 (not assignable); (5) Bayer AG, 1989c

5.4.1 Acute Oral Toxicity

The oral LD50 values reported for CAS No. 81-11-8 at SIAM 4 were 3000 mg/kg in the rat and 47000 mg/kg in the guinea pig. The oral LD50 value reported for the related material CAS No. 7336-20-1 is > 5000 mg/kg in the male rat. A rat oral LD50 value of > 16000 mg/kg CAS No. 3709-43-1 was reported in IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000. The primary reference was not stated and was not able to be located. Therefore, the study was assigned a reliability rating of 4 (not assignable). In a guideline, GLP study, the related material CAS No. 78447-91-3 had an oral LD50 value in the rat of > 2000 mg/kg bw.

5.4.2 Acute Inhalation Toxicity

No studies were located.

5.4.3 Acute Dermal Toxicity

No studies were located.

5.4.4 Irritation/Sensitization

Results of irritation /sensitization tests performed with the category members are shown in Table 8.

Table 8. Irritation/Sensitization of Stilbene Intermediates Category

Chemical	Skin Irritation (not required)	Eye Irritation (not required)	Sensitization (not required)
81-11-8	Not irritating	None to moderate	No data
7336-20-1	Not irritating	None to moderate	No data
3709-43-1	Not irritating	Not irritating	No data
78447-91-3	Not irritating	Not irritating	No data

Bolded type represents category members; regular type represents the surrogate with supporting data.

Irritation

OECD Test Guideline 404 and 405 studies performed in rabbits indicate that CAS Nos. 81-11-8, 7336-20-1, 78447-91-3 and a formulated product containing 60% CAS No. 3709-43-1 and 35% water are not irritating to skin or eyes (Krotlinger, 1993a,b; Ciba-Geigy Limited, 1986a,b; Bayer

AG 1989d). Additional studies that were not available for review but are cited in European IUCLID documents indicate moderate eye toxicity for CAS No. 81-11-8 and 7336-20-1 (RTECS, no date listed).

Sensitization

No studies were located.

5.4.5 Repeated-Dose Toxicity

Repeated dose toxicity studies that have been performed with the category members are summarized in Table 9 below.

The repeated dose toxicity of CAS No. 7336-20-1 has been tested in rats and mice by the NTP (USDHHS, 1992). This study was used to fill the repeated dose toxicity endpoint for CAS No. 81-11-8 at SIAM 4. Dietary doses administered to rats and mice in a 13 week study were 6250, 12500, 25000, 50000 and 100000 ppm. The 13-week NOAELs in the rat and mouse were 25000 (approximately 1529 and 1715 mg/kg/day for males and females, respectively) and 12500 ppm (approximately 1738 and 2081 mg/kg/day for males and females, respectively). Mean body weight gain was decreased in male rats and female mice receiving 50,000 or 100000 ppm, in male mice receiving doses ≥ 25000 ppm, and in female rats receiving 100000 ppm. Clinical findings in rats given 50000 or 100000 ppm and mice given 100000 ppm included diarrhea, emaciation, and hyperemia of the perineum. Histopathologic lesions in rats ingesting 100000 ppm were bone marrow hypercellularity and chronic inflammation of the anus and rectum. Similar changes in the anus and /or rectum were observed in mice ingesting concentrations ≥ 50000 ppm. Male mice receiving 100000 ppm had atrophy of the thymus and females receiving this dose exhibited atrophy of the uterus and ovaries.

In 2 year studies, 12500 and 25000 ppm CAS No. 7336-20-1 were tested in rats and 6250 and 12500 ppm 7336-20-1 were tested in mice. These studies were also reviewed for CAS No. 81-11-8 at SIAM 4. In the 2 year study, the NOAELs in the rat and mouse were 12500 and 6250 ppm, respectively (approximately 765 and 1400 mg/kg/day, respectively). At study termination,

Table 9. Repeated Dose Toxicity for Stilbene Intermediates Category

Category Member	Species/ Exposure	Dose [a]	Gross Changes	Histopathological Changes
81-11-8	Data for 7336-20-1 used at SIAM 4			
7336-20-1 (USDHHS, 1992)	F344 rat, oral feed, 2 years, 12500 and 25000 ppm	12500 [b] 25000 [c]	None ↓ bw, males	None related to treatment
(USDHHS, 1992)	F344 rat, oral feed, 13 weeks, 6250, 12500, 25000, 50000, 100000 ppm	6250 12500 25000 [b] 50000 [c] 100000	None None None ↓ bw, diarrhea, emaciation, red anus ↓ bw, food, emaciation, red anus, diarrhea	None None None None Inflammation in rectum and anus, hypercellularity of bone marrow
(USDHHS, 1992)	B6C3F1 mouse, oral feed, 2 years, 6250 and 12500 ppm	6250 [b] 12500 [c]	None ↓ bw (females)	None None
(USDHHS, 1992)	B6C3F1 mouse, oral feed, 13 weeks, 6250, 12500, 25000, 50000, 100000 ppm	6250 12500 [b] 25000 [c] 50000 100000	None None ↓ bw (males) ↓ bw, changes in organ weights Increased mortality (males), ↓ bw, ↑ feed, diarrhea, emaciation, lethargy, tremors	None None Inflammation in rectum and anus Inflammation in rectum and anus Inflammation in rectum and anus, atrophy of thymus (males), uterus and ovaries
3709-43-1	No data			
78447-91-3	No data			

Bolded type represents category members; regular type represents the surrogate with supporting data.
[a] Dose is in ppm unless listed otherwise; [b] NOAEL; [c] LOAEL

mean body weights were marginally decreased for male rats receiving 25000 ppm and female mice receiving 12500 ppm. Feed consumption and survival were not affected by treatment and no abnormal clinical findings were noted in treated animals. There was no effect of treatment on the incidences of neoplasms in rats and mice.

5.4.6 Genetic Toxicity: Gene Mutations and Chromosome Aberrations

Genetic toxicity tests that have been performed with the category members are listed in Table 10.

Table 10. Genotoxicity of Stilbene Intermediates Category

Category Member	Ames Test (w/wout activation)	Cytogenicity (CHO cells)
81-11-8	Negative (1)	Negative (2)
7336-20-1	Negative (3)	Negative (3)
3709-43-1	No data	No data
78447-91-3	Negative (4) Ambig (E. coli) (5)	No data

Bolded type represents category members; regular type represents the surrogate with supporting data.
(1) Zeiger et al. 1987; (2) Loveday et al., 1990; (3) USDHHS, 1992; (4) Herbold, 1992; (5) Norpoth, 1977a,b

Mutations

Up to 5000 micrograms/plate CAS No. 81-11-8, 7336-20-1 and 78447-91-3 tested negative for mutagenicity in S. typhimurium strains TA98, TA100, TA1535 and TA1537 in the presence and absence of metabolic activation (Zeiger et al., 1987, Herbold, 1992; USDHHS, 1992). CAS No. 81-11-8 tested negative and CAS No. 78447-91-3 had an ambiguous result in E. coli WP2uvrA (Norpoth, 1977a,b). The aforementioned studies for CAS No. 81-11-8 and 7336-20-1 were reviewed at SIAM 4.

Chromosome Aberrations

CAS No. 81-11-8 tested negative for chromosome aberrations and sister chromatid exchanges in Chinese Hamster Ovary (CHO) cells at concentrations up to approximately 1000 micrograms/ml (Loveday et al., 1990). These studies were not described in the dossier accepted at SIAM 4. The study that was reviewed at SIAM 4 was a negative CHO study for CAS No. 7336-20-1 (USDHHS, 1992).

5.4.7 Carcinogenicity

In a 2 year feeding study, concentrations of CAS No. 7336-20-1 of up to 25,000 ppm (approximately 1000 mg/kg/day for the majority of the study) and 12,500 ppm (approximately 500 mg/kg/day for the majority of the study) had no effect on the incidences of neoplasms at any

site in rats and mice, respectively (USDHHS, 1992). This study was reviewed at SIAM 4 (for CAS No. 81-11-8).

5.4.8 Reproductive Toxicity

CAS No. 81-11-8 was tested in an OECD Preliminary Reproductive Screen at doses of 40, 200 and 1000 mg/kg/day. This study was reviewed at SIAM 4. The test material had no effect on clinical signs, body weight changes, food consumption or necropsy findings in male or female Sprague-Dawley rats. Testicular and epididymal weights and histopathology in treated animals were similar to controls. There was no effect of treatment on any reproductive or offspring parameter measured (MHW, Japan, 1994).

In a 13-week repeated dose, dietary study, all female mice receiving 100000 ppm CAS No. 7336-20-1 exhibited endometrial atrophy of the uterus and atrophy of the ovaries (USDHHS, 1992). This was not observed at lower doses in mice and was not observed in female rats receiving up to 100000 ppm.

5.4.9 Developmental Toxicity

In the OECD Preliminary Reproductive Screen with CAS No. 81-11-8 that was reviewed at SIAM 4, there was no effect of treatment with up to 1000 mg/kg/day from 14 days prior to mating to lactation day 3 on number of offspring (total or live), sex ratio, live birth index, viability index, or body weight. No abnormal findings attributable to the test substance were noted in external examination, clinical signs or necropsy of the offspring (MHW, Japan, 1994).

5.4.10 Other Effects

Studies conducted in cohorts of male workers employed in a factory manufacturing CAS No. 81-11-8 have suggested the possibility of a testosterone-lowering effect of CAS No. 81-11-8 (Grajewski et al., 1996; Quinn et al., 1990; Whelan et al., 1996). When interviewed, there were reports of loss of libido and potency. Since the studies were conducted on a small scale and

there was no clear relationship between testosterone level and reported symptoms of low/libido potency, the reliability of the studies is questionable. None of these studies were reviewed for SIAM 4.

CAS No. 81-11-8 has been tested for uterotrophism in weanling female rats (Smith and Quinn, 1992). Groups of 5-25 animals were injected intraperitoneally with 0.1, 1, 10, 30, 100, 300 or 1000 mg/kg test material (or 10 ml/kg saline vehicle) or administered the same doses by oral gavage using a fixed volume of 10 or 30 ml/kg. Uterus weights of animals given 300 or 1000 mg/kg material i.p. or 1000 or 3000 mg/kg orally were significantly greater than control, suggesting that the material possesses uterotropic activity. However, the variability of the control uterine weights in the i.p. study questions the validity of the results.

The possibility of an uterotropic effect of CAS No. 7336-20-1 also was tested in female rats. Once daily subcutaneous injection of 10 or 30 mg/animal (approx. 230 or 750 mg/kg bw) for 3 days had no effect on uterus weight (Hostetler et al., 1996). In rats and mice administered up to 100000 ppm CAS No. 7336-20-1 in the diet for 13 weeks and up to 12500 ppm (mice) and 25000 ppm (rats) for 2 years, there is no evidence of uterotrophism (USDHHS, 1992). Conversely, uterine weights of mice administered 100000 ppm for 13 weeks were less than control, in keeping with the observation of reduced body weight. In vitro studies on relative binding affinity of the synthetic estrogen diethylstilbestrol (DES) and CAS No. 7336-20-1 to the human estrogen receptor in a breast cell line were positive and negative (respectively), indicating that CAS No. 7336-20-1 does not possess estrogenic activity (unlike DES) (Hostetler et al., 1996).

In conclusion, although some reports suggest that CAS No. 81-11-8 causes uterotrophism, more reliable studies with the sodium salt of the molecule (CAS No. 7336-20-1) indicate that this material does not possess estrogenic activity.

5.4.11 Test Plan for Mammalian Toxicity

Adequate oral acute toxicity tests performed on all category members indicate that members of this category are of low acute toxicity. Although not required, skin and eye irritation studies have been performed on the majority of the category members. These studies show that the materials are generally not irritating to skin and are slightly to moderately irritating to eyes. Repeated dose toxicity studies performed CAS No. 7336-20-1 indicate 13-week dietary NOAELs of > 1500 mg/kg/day in rats and mice. No additional acute or repeated dose toxicity testing is planned.

Ames and mammalian cell mutation tests performed on the category members were all negative, with the exception of an ambiguous result with CAS No. 78447-91-3 in E. coli. In vitro cytogenicity studies performed on CAS Nos. 81-11-8 and 7336-20-1 were negative. These data, along with the negative result of a long term toxicity/carcinogenicity tests performed on CAS No. 7336-20-1 indicate a low potential for these materials for genetic toxicity. No additional genetic toxicity testing is planned.

A reproductive toxicity test performed on CAS Nos. 81-11-8 showed no effect of treatment with 1000 mg/kg on fertility of rats. No embryotoxic or teratogenic effects were reported in rabbits treated with up to 1000 mg/kg CAS Nos. 81-11-8 or 7336-20-1. In conclusion, results of reproductive/developmental toxicity testing indicate that these materials are not selectively toxic to the reproductive system or developing fetus.

6. Summary

Physical properties

Adequate measured information are available for melting points, which are high (>200-300 degrees C) and consistent with the category members being organic salts. As metal organic salts or inner salts, the category members exist in ionic form and not as discrete molecules. Therefore, these materials do not boil without first undergoing decomposition at or above their melting points. Nor do they exert significant vapor pressure, other than that attributable to volatile impurities or additives that may be present, such as water. Sufficient estimated data predict that log Pow values of the category members will be low or negative (Range 0.2 to –

3.00). Water solubilities determined for three category members or surrogates are adequate to predict the water solubility of the remaining member for which data are not available. No further testing is therefore planned for physical properties

Environmental fate properties

Members of this category are not readily biodegradable. Since category members do not volatilize, atmospheric photodegradation is not an important degradative pathway, and conducting atmospheric photodegradation modeling or studies would not be useful. Available data indicate that these materials undergo photodegradation in the hydrosphere as well as slow biodegradation. Level III fugacity modeling indicates that when released to the environment, category members will partition predominately to soil and water, and negligibly to the atmosphere. Further environmental fate testing is not planned.

Aquatic toxicity

Adequate fish and invertebrate toxicity tests have been performed on the majority of the category members. LC/EC50 values in fish and Daphnia magna are > 100 mg/l. Algae toxicity studies performed with CAS Nos. 81-11-8 and 7336-20-1 indicate EC50 values ≥ 76 mg/l. The results indicate a low potential of toxicity towards aquatic species. Results of Daphnia and algae toxicity studies with CAS Nos. 81-11-8 and 7336-20-1 are expected to be predictive of those for CAS No. 3709-43-1. No additional aquatic testing is necessary.

Mammalian toxicity

Adequate tests have been performed for the acute toxicity, repeated dose toxicity, and genetic toxicity endpoints. All reproductive/developmental toxicity tests that have been conducted indicate that these materials are not reproductive or developmental toxicants.

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APPENDIX

STILBENE-BASED FLUORESCENT WHITENING AGENTS MANUFACTURED FROM STILBENE INTERMEDIATES (CATEGORY MEMBERS)

CAS No.	Chemical Name	Common or Trade Name
4404-43-7	4,4'-Bis(6-anilino-1,4-bis(2-hydroxyethyl)amino)-1,3,5-triazin-2-yl)amino)stilbene-2,2-disulfonic acid	C.I. Fluorescent Brightener 28/113, Free acid
4193-55-9	Disodium 4,4'-bis(6-anilino-1,4-bis(2-hydroxyethyl)amino)-1,3,5-triazin-2-yl)amino)stilbene-2,2-disulphonate	C.I. Fluorescent Brightener 28/113, Disodium salt
70942-01-7	potassium sodium 4,4'-bis[6-anilino-4-[bis(2-hydroxyethyl)amino]-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate	C.I. Fluorescent Brightener 28/113
13863-31-5	2,2'-Stilbenedisulfonic acid, 4,4'-bis((4-anilino-6-((2-hydroxyethyl) methyl amino) –s-triazin-2-yl)amino)-, disodium salt	Tinopal 5BM
16090-02-1	disodium 4,4'-bis[(4-anilino-6-morpholino-1,3,5-triazin-2-yl) amino]stilbene-2,2'-disulphonate	C.I. Fluorescent Brightener 260, Disodium salt C.I. Fluorescent Brightener 339
16470-24-9	tetrasodium 4,4'-bis[[4-[bis(2-hydroxy ethyl)amino]-6-(4-sulphonatoanilino)-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate]	C.I. Fluorescent Brightener 220, Tetrasodium salt
67786-25-8	tetrasodium 4,4'-bis[[4-[bis(2-hydroxy propyl)amino]-6-[(4-sulphonato phenyl)amino]-1,3,5-triazin-2-yl]amino]-stilbene-2,2'-disulphonate	C.I. Fluorescent Brightener 263, Tetrasodium salt
29637-52-3	2,2'-Stilbenedisulfonic acid, 4,4'-bis[[4-[(2-carbamoylethyl)(2-hydroxyl ethyl)amino]-6-(p-sulfoanilino)-s-triazin-2-yl]amino]-,tetrasodium salt	C.I. Fluorescent Brightener 235, Tetrasodium salt

ETAD North America Stilbene Fluorescent Brighteners Intermediates

HPV Submission

December 21, 2005

201-16114

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1. **Test Plan and Category Justification (29 pp.)**

H:\SWAs\Test Plan
Stilbene Intermediate

2. **CAS 81-11-8 (Category Member). IUCLID Data Set (60 pp.)**

H:\SWAs\Interded
iuclid81118Aug29200

3. **CAS 7336-20-1 (Category Member). IUCLID Data Set (51 pp.)**

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IUCLID7336201Dec1(

4. **CAS 3709-43-1 (Category Member). IUCLID Data Set (23 pp.)**

H:\SWAs\Intermed
IUCLID3709431Aug 2

5. **CAS 78447-91-3 (Surrogate with supporting data). IUCLID Data Set (24 pp.)**

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201-16114

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IUCLID

Data Set

Existing Chemical	:	ID: 81-11-8
CAS No.	:	81-11-8
EINECS Name	:	4,4'-diaminostilbene-2,2'-disulphonic acid
EC No.	:	201-325-2
TSCA Name	:	Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis[5-amino-
Molecular Formula	:	C14H14N2O6S2

Producer related part

Company	:	PCA Services, Inc
Creation date	:	24.05.2004

Substance related part

Company	:	PCA Services, Inc
Creation date	:	24.05.2004
Status	:	
Memo	:	
Printing date	:	29.08.2005
Revision date	:	29.08.2005
Date of last update	:	29.08.2005
Number of pages	:	61
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	
Name	:	3V SIGMA S.p.A.
Contact person	:	
Date	:	
Street	:	R & D Dept - Via A. Moro 28
Town	:	MOZZO (BERGAMO)
Country	:	Italy
Phone	:	19 39 35 611 334
Telefax	:	19 39 35 461 512
Telex	:	
Cedex	:	I - 24030
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type	:	
Name	:	3V Sigma S.p.A.
Contact person	:	
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Telefax	:	(35) 46 15 12
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type	:	
Name	:	Bayer AG
Contact person	:	
Date	:	
Street	:	
Town	:	51368 Leverkusen
Country	:	Germany
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type	:	
Name	:	Hickson & Welch Ltd.
Contact person	:	
Date	:	
Street	:	Wheldon Road
Town	:	WF10 2JT Castleford
Country	:	United Kingdom
Phone	:	
Telefax	:	

Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Type	:	
Name	:	VIOCHROM SA
Contact person	:	
Date	:	
Street	:	3 EL.VENIZELOU STR.
Town	:	GR123-51 AGHIA VARVARA ATHENS
Country	:	Greece
Phone	:	301-5393120-124
Telefax	:	5392634
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	
Substance type	:	organic
Physical status	:	solid
Purity	:	
Colour	:	
Odour	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

2,2'-(1,2-ETHENEDIYL)BIS[5-AMINOBENZENESULFONIC ACID]

Source	:	VIOCHROM SA AGHIA VARVARA ATHENS EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

2,2'-DISULFO-4,4'-STILBENEDIAMIN

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

4,4'-DIAMINO-2,2'-(1,2-ETHENDIYL)BIS(5-AMINOBENZOLSULFONSAEURE)

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

4,4'-DIAMINO-2,2'-STILBENDISULFONSAURE

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

4,4'-DIAMINOSTILBEN-2,2'-DISULFONSAEURE

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

4-4' Diamino-2,2'-stilbendisulfonic acid, L flavonic acid

Source : 3V SIGMA S.p.A. MOZZO (BERGAMO)
3V Sigma S.p.A. Mozzo Bergamo
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Amsonic acid

Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

BENZENESULFONIC ACID, 2,2'-(1,2-ETHENEDIYL)BIS(5-AMINO-

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

BENZENESULFONIC ACID, 2,2'-(1,2-ETHENEDIYL)BIS[5-AMINO-

Source : VIOCHROM SA AGHIA VARVARA ATHENS
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

DAS

Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

DASD

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

DASDSA

Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Flavonic acid

Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

FLAVONSAEURE L

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

P,P'-DIAMINODIPHENYLETHYLEN-O,O'-DISULFONSAEURE

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

P,P'-DIAMINOSTILBEN-O,O'-DISULFONSAEURE

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 10000 - 50000 tonnes in

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Remark : All data in this section were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000. No reliability ratings were assigned.

Type of use : type
Category : Non dispersive use

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : type
Category : Wide dispersive use

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : industrial
Category : Chemical industry: used in synthesis

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : industrial
Category : Public domain

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : use
Category : Bleaching agents

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : use
Category : Cleaning/washing agents and disinfectants

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : use
Category : Coloring agents

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : use
Category : Intermediates

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : other
Limit value : 10 mg/m3

Remark : Submitter is not aware of any assigned occupational exposure limit value.
UK nuisance dust OES
Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by	:	other: Bayer AG
Labelled by	:	other: Bayer AG
Class of danger	:	1 (weakly water polluting)
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation	:	
Substance listed	:	no
No. in Seveso directive	:	
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

1.8.5 AIR POLLUTION

Classified by	:	other: no classification
Labelled by	:	
Number	:	
Class of danger	:	
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark	:	Substance is produced by reduction of 4,4'-dinitrostilbene-2,2'-disulphonic acid. Exposure in the workplace can occur by inhalation of dust or by ingestion. There is little evidence of absorption through the intact skin. There are no data available quantifying exposure in our own workplace.

Release to the Environment could occur principally as a result of spillages.

The submitter knows of only one manufacturing site in the UK. Substance is manufactured in Germany and Italy in the EU and in the USA and Japan.

Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

1.11 ADDITIONAL REMARKS

Remark : Substance is not classified as dangerous according to International Transport criteria and consequently is not subject to any specific control measures during transport.

Substance is typically packed in paper sacks of ca. 20 kg net weight, and 18 to a pallet. Smaller quantities are despatched as an aqueous solution in 18 Tonne Road Tankers within the UK.

Source : Hickson & Welch Ltd. Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : > 300 °C
Sublimation :
Method : other
Year : 1994
GLP : yes
Test substance :

Source : SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability : (2) valid with restrictions
Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag : Critical study for SIDS endpoint
01.08.2004 (18)

Value : > 300 °C
Sublimation :
Method : other
Year : 1948
GLP : no data
Test substance : as prescribed by 1.1 -1.4

Remark : This study was briefly summarized in the OECD dossier for SIAM 4. It has been edited to be in conformance with new guidelines.
Method : The melting point was determined after purification of the substance by crystallization as fine yellowish needles. The melting point was presumably determined by gradually heating the test material to 300 degrees in a capillary tube immersed in a hot oil bath, which was the standard technique at the time of the publication.
Reliability : (2) valid with restrictions
Published value. Test method details were not provided by authors.
01.08.2004 (10)

2.2 BOILING POINT

Remark : No data available.

2.3 DENSITY

Type : relative density
Value : = 2.45 at 20 °C
Method : other
Year :
GLP : no data
Test substance :

Source : SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability : (2) valid with restrictions
Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
01.08.2004 (7)

Type : bulk density
Value : ca. 500 - 600 kg/m3 at 20 °C
Method :

Year	:	
GLP	:	no data
Test substance	:	
Source	:	3V SIGMA S.p.A. MOZZO (BERGAMO) 3V Sigma S.p.A. Mozzo Bergamo EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.
01.08.2004		
Type	:	bulk density
Value	:	300 - 600 kg/m3 at 25 °C
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.
01.08.2004		(3)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	at 25 °C
Decomposition	:	
Method	:	OECD Guide-line 104 "Vapour Pressure Curve"
Year	:	1994
GLP	:	yes
Test substance	:	
Result	:	Value was < 130 Pa. (<1.3 hPa)
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag	:	Critical study for SIDS endpoint
08.07.2004		(18)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	-1.7 at °C
pH value	:	
Method	:	other (calculated): CLOGP-3.54 MedChem Software 1989.
Year	:	
GLP	:	
Test substance	:	
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

01.08.2004 (4)

Partition coefficient :
Log pow : -2.5 at °C
pH value :
Method : other (calculated): CLOGP-3.54 MedChem Software 1989.
Year :
GLP :
Test substance :

Source : SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability : (2) valid with restrictions
Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
01.08.2004 (13)

Partition coefficient :
Log pow : at 25 °C
pH value :
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1994
GLP : yes
Test substance :

Remark : The Log Pow was not measurable due to poor solubility in both water and octanol.
Source : SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability : (2) valid with restrictions
Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
01.08.2004 (18)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 32 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : of very low solubility
Stable :
Deg. product :
Method : OECD Guide-line 105
Year : 1994
GLP : Yes
Test substance :

Source : SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability : (2) valid with restrictions
Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag : Critical study for SIDS endpoint
01.08.2004 (18)

Solubility in : Water
Value : ca. .65 g/l at 20 °C

pH value	:	
concentration	:	
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	of very low solubility
Stable	:	
GLP	:	no data
Remark	:	No details are provided.
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

01.08.2004 (3)

Solubility in	:	
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	other: very slightly soluble in water
Stable	:	
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Published data in a reference book.

01.08.2004 (28)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	water
Light source	:	Sun light
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Test substance	:	
Remark	:	Spectrum of substance: Epsilon = 1.61 x 10E4 at 300 nm; Epsilon = 3.32 x 10E4 at 340 nm Estimated parameter for calculation: Quantum Yield = 0.001 Concentration = 5 x 10E-5 M Depth of Water Body: 500 cm Conversion Constant: 6.023 x 10E20
Result	:	Degradation Rate: 6.19 x 10E-11 mol/l/s Half Life: 1.78 x 10E-2 years
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag	:	Critical study for SIDS endpoint

07.07.2004 (16)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	1994
GLP	:	yes
Test substance	:	
Result	:	Stable at pH 4, 7 and 9 at 25 degrees C
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag	:	Critical study for SIDS endpoint

01.08.2004 (18)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other: air, water, soil, biota
Air	:	0 % (Fugacity Model Level III)
Water	:	57.8 % (Fugacity Model Level III)
Soil	:	42.1 % (Fugacity Model Level I)
Biota	:	.107 % (Fugacity Model Level II/III)
Method	:	other: calculation using EPIWIN v3.11
Year	:	2005
Test substance	:	as prescribed by 1.1 – 1.4
Result	:	Half-lives in various media are air: 1.18 hours; water: 900 hours; soil: 900 hours; and sediment: 3600 hours. The Henry's Law Constant [calculated by EPIWIN HENRY (v3.10)] is 3.37 E-24 atm-m3/mol (bond est.). The soil-sediment coefficient [calculated by EPIWIN PCKOC (v1.66)] is Koc = 4845.
Test condition	:	Inputs to the model are CAS No. 81-11-8 and emission rates: air: 0 kg/hr, water: 1000 kg/hr, and soil: 1000 kg/hr.
Reliability	:	(2) valid with restrictions Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	100 mg/l related to DOC (Dissolved Organic Carbon) related to
Kinetic of test subst.	:	% 7 day(s) 0 % 14 day(s) 0 % 21 day(s) 0 % 28 day(s) 5 %
Control substance	:	Aniline
Kinetic	:	% %
Deg. product	:	
Method	:	OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year	:	1989
GLP	:	no
Test substance	:	as prescribed by 1.1 -1.4
Remark	:	A summary for this study does not appear in the OECD dossier. Available data were translated from German to English.
Result	:	The DOC net for the test material at 3 hours and 1, 7, 14, 21, 27 and 28 days was 0%, 6%, 0%, 0%, 0%, 6% and 5%, respectively. At the same times, biodegradation of the positive reference material was 11%, 30%,

97%, 100%, 100%, 99% and 96%, respectively.

Test condition	:	DOC (dissolved oxygen concentration) concentration of the test substance: 415 mg/l Stock solution: 1 g/l Theoretical DOC in the test substance: 100 mg/l Amount charged: 83.5 ml/l, no adaptation Analytical: DOC determination Amount of test probe: 20 ml Toxicity of the test substance: not tested The DOC net for the reference substance and test material were obtained by subtracting the DOC of a blank from the DOC values for the reference material and test material.
Test substance	:	Minimum purity was 94%.
Reliability	:	(2) valid with restrictions Basic data given.
Flag	:	Critical study for SIDS endpoint

19.07.2004 (1)

Type	:	aerobic
Inoculum	:	other: Japanese standard activated sludge
Concentration	:	100 mg/l related to Test substance related to
Contact time	:	
Degradation	:	(±) % after
Result	:	under test conditions no biodegradation observed
Deg. product	:	
Method	:	OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year	:	1994
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Degree of degradation after 28 days: 0,0 and 0% from BOD 4,1 and 3% from HPLC analysis
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag	:	Critical study for SIDS endpoint

19.07.2004 (18)

Type	:	aerobic
Inoculum	:	predominantly domestic sewage, adapted
Contact time	:	
Degradation	:	0 (±) % after 20 day(s)
Result	:	under test conditions no biodegradation observed
Deg. product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	1977
GLP	:	no
Test substance	:	other TS: ca. 98 %
Remark	:	Emulgator W used as emulsifier
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test condition	:	concentrations: 0.8; 2.4; 8; 24 mg/l
Reliability	:	(4) not assignable

Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

3.6 BOD5, COD OR BOD5/COD RATIO

Remark : ThOD: 1483 mg/g
DOC: 415 mg/g

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

01.08.2004 (2)

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Oryzias latipes (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	> 1000
Limit test	:	
Analytical monitoring	:	no
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The LC50 values for 24, 48, 72 and 96 hr were all > 1000 mg/l.
Test condition	:	Groups of 10 fish were exposed to each of 5 nominal concentrations (95-1000 mg/l) and a laboratory water control in open systems.
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Test substance	:	Purity of the test material was 96.4%
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag	:	Critical study for SIDS endpoint

07.07.2004 (6)

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC0	:	= 200
Source	:	Bayer, unpublished data SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

01.08.2004

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC0	:	200
Limit test	:	
Analytical monitoring	:	no
Remark	:	It is likely that this is the same study as referred to above.
Method	:	other: Bestimmung der akuten Wirkung von Stoffen auf Fische. Arbeitskreis "Fischtest" im Hauptausschuss "Detergentien" (15.10.73) [Translated as, “Determination of Acute Effect of Substance on Fish. Work realm “Fish test in the Important Application ‘Detergents’ (15.10.73).”]
Year	:	1975
GLP	:	no
Test substance	:	other TS: ca. 98 %
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable

Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

01.08.2004 (2)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	= 210
Analytical monitoring	:	no
Method	:	OECD Guide-line 202
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The 24 hour EC50 value (with 95% confidence limits) was 130-250 mg/l.
Test condition	:	Twenty daphnids (4 replicates, 5 organisms per replicate) were exposed to each of 5 nominal concentrations (100-1000 mg/l). The stock solution was prepared with DMSO:HCO (9:1). Controls with and without the vehicle were tested.
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Test substance	:	Purity of the test material was 96.4%
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag	:	Critical study for SIDS endpoint

07.07.2004 (6)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	= 32
EC50	:	= 76
Limit test	:	
Analytical monitoring	:	no
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	Selenastrum capricornutum ATCC 22622 were used in the test. The stock solution was prepared in DMSO (100 mg/l). Controls with and without the vehicle were tested. The EC50 values for biomass were calculated based on 7 nominal concentrations (10-320 mg/l). An open system was used.
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Test substance	:	Purity of the test material was 96.4%
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag	:	Critical study for SIDS endpoint

07.07.2004 (6)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	Pseudomonas fluorescens (Bacteria)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	1000
Analytical monitoring	:	no
Method	:	other: Bestimmung der biologischen Schadwirkung toxischer Abwaesser gegen Bakterien. DEV, L 8 (1968) modifiziert. [Translated as, "Determination of the Biological Harmful Effect of Toxic Wastewater Against Bacteria. DEV, L 8 (1968) Modified."]
Year	:	1975
GLP	:	no
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	The purity of the material is listed as 96.4% in the OECD dossier and 98% in the European Commission dossier.
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website. Additional information was obtained from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

01.08.2004 (2)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species	:	Daphnia magna (Crustacea)
Endpoint	:	other: immobility and reproduction rate
Exposure period	:	21 day(s)
Unit	:	mg/l
Analytical monitoring	:	no
Method	:	other: OECD Test Guideline 202
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Immobility: EC50 (48 hr) = 130 mg/l (95% confidence limits: 110-140 mg/l) EC50 (21 days) = 74 mg/l (95% confidence limits: 63-86 mg/l) Reproduction: EC50 (21 days) = 92 mg/l (95% confidence limits: 85-98 mg/l) NOEC = 37 mg/l ($p < 0.05$) LOEC = 67 mg/l ($p < 0.05$)
Test condition	:	Forty daphnids (10 organisms per replicate, 4 replicates) were exposed to each of 5 nominal concentrations (21-210 mg/l) in a semi-static, open system. Immobility and reproduction rate were monitored for 21 days.
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Test substance	:	Purity of the test material was 96.4%
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

07.07.2004 (6)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

Type : animal
Deg. product :

Result : 97% eliminated via urinary excretion (i.v.infusion)
Radiolabel recovery in faeces after oral administration: 80 to 92%.
Source : 3V SIGMA S.p.A. MOZZO (BERGAMO)
3V Sigma S.p.A. Mozzo Bergamo
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

01.08.2004

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: Di-sodium salt (7336-20-1)
Remark	:	No symptoms
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.
Flag	:	Critical study for SIDS endpoint

07.07.2004 (14)

Type	:	LC0
Value	:	ca. 3000 mg/kg bw
Species	:	rat
Strain	:	Sprague Dawley
Sex	:	female
Number of animals	:	
Vehicle	:	
Doses	:	1000 and 3000 mg/kg
Method	:	other
Year	:	1992
GLP	:	no data
Test substance	:	As prescribed by 1.1 – 1.4
Remark	:	A summary for this study does not appear in the OECD dossier.
Result	:	No signs of toxicity were noted.
Test condition	:	The rats were housed in groups of 3-6 animals and were allowed free access to food and water. Single oral doses of 1000 or 3000 mg/kg were given to an unlisted number of animals. Toxicity was assessed 24 hour later.
Reliability	:	(2) valid with restrictions Basic data given

08.07.2004 (23)

Type	:	LD50
Value	:	= 47000 mg/kg bw
Species	:	guinea pig
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	unknown

Year	:	1980
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	Function of liver and kidney were impaired. Ureter and bladder were also affected.
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

07.07.2004 (29)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	other
Value	:	ca. 3000 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	female
Number of animals	:	6
Vehicle	:	
Doses	:	
Method	:	
Year	:	1992
GLP	:	no data
Test substance	:	As prescribed by 1.1 – 1.4
Remark	:	A summary for this study does not appear in the OECD dossier. Two out of six animals given 3000 mg/kg i.p. died within 24 hours of treatment. None of the 15 animals given 1000 mg/kg died.
Reliability	:	(2) valid with restrictions Basic data given

08.07.2004 (23)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	500 mg
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	3
Vehicle	:	water
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark	:	A summary for this study does not appear in the OECD dossier. Only three animals were tested in accordance with the German Animal Protection Act.
Result	:	All scores were 0. The material was not irritating to the skin.
Test condition	:	Animals: Three healthy, adult, nulliparous, nonpregnant, female rabbits (strain HC:NZW) weighing 3.4, 3.6 and 4.0 kg were used in the study. They were quarantined for at least 14 days before use. During this period, pooled feces specimens were examined for Coccidia oocysts. Rabbits were individually housed in stainless steel cages under standardized conventional conditions (21 +/- 1.5 degrees C, 40-70% relative humidity, 12 hour light/dark cycle, 500 lux illumination, 12-15 air exchanges per hour). They were fed 100-120 g standard diet per animal/day and allowed free access to tap water. The animals were examined one day prior to use. Only animals not exhibiting any alterations to skin or eyes were used. Test conduct: Approximately 24 hours before the test, fur was clipped from the dorso-lateral area of the trunk (6 x 6 cm) of each of the rabbits. Care was taken to avoid abrasion. Pulverized test material (500 mg) was moistened with deionized water and applied to a hypoallergenic patch. An additional patch as moistened only with water. The patches were placed on the opposite dorso-lateral areas of the trunk of each animal. They were held in place with a semiocclusive dressing for 4 hours. The area of exposure was approximately 6 cm2. After 4 hours, dressings were removed and the exposed skin was carefully washed with water. Dermal irritation was scored for the degree of erythema/eschar formation according to the method of Draize after 1, 24, 48, and 72 hours and 7 days. Erythema/eschar and edema were each scored on a scale of 0-4 (no effect to severe effect). Any serious lesions or toxic effects other than dermal irritation were recorded. The Draize scores at 24, 48 and 72 hours were added. The total of the three scores was divided by three to give the irritation index. This index was calculated separately for erythema/eschar formation and edema. Data interpretation was based on the individual indices of the two most sensitive animals. All study-related documentation was archived, in compliance with GLP.
Reliability	:	(2) valid with restrictions Guideline study. However, test material purity was not listed.

19.07.2004 (12)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	
Year	:	
GLP	:	
Test substance	:	

Source	:	3V Sigma S.p. A. Mozzo (Bergamo)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

20.07.2004 (21)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	39 other: mg
Exposure time	:	24 hour(s)
Comment	:	
Number of animals	:	3
Vehicle	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A summary for this study does not appear in the OECD dossier. Only three animals were tested in accordance with the German Animal Protection Act.
Result	:	Conjunctival redness scores of 1 (some blood vessels definitely hyperemic) were observed at 1 and 24 hours in all rabbits and also at 48 hours in one rabbit. Discharge scores of 1 (slightly increased) were observed in 2 rabbits at 1 hour. Swelling scores of 1 (swelling slightly above normal, including nictitating membrane) were observed in 2 rabbits at 1 hour. All other scores were 0. The irritation indices in the 3 rabbits were 0.3, 0.3 and 0.7. Scores < 1 were considered to be indicative of no irritation.
Test condition	:	Animals: Three healthy, adult, nulliparous, nonpregnant, female rabbits (strain HC:NZW) weighing 2.9, 3.4 and 3.4 kg were used in the study. They were quarantined for at least 14 days before use. During this period, pooled feces specimens were examined for Coccidia oocysts. Rabbits were individually housed in stainless steel cages under standardized conventional conditions (21 +/- 1.5 degrees C, 40-70% relative humidity, 12 hour light/dark cycle, 500 lux illumination, 12-15 air exchanges per hour). They were fed 100-120 g standard diet per animal/day and allowed free access to tap water. The animals were examined one day prior to use. Only animals not exhibiting any alterations to skin or eyes were used. Test conduct: The lower lid was gently pulled away from the eyeball and a volume of 100 microliters of pulverized test material (approximately 39 mg) was placed into the conjunctival sac of one eye of each of the rabbits. The lids were then gently held together for about 1 second. The other eye remained untreated and served as the control. The treated eye was rinsed with normal saline 24 hours after treatment. Eye irritation was scored and recorded at 1, 24, 48, and 72 hours and 7 days. The signs of cornea (opacity and area affected), iris (hyperemia, reaction to light), conjunctivae (erythema, chemosis), and discharge were recorded as described by Draize. The aqueous humor was scored for opacity as described by McDonald and Shadduck (in: Marzulli FN and Maibach HI (Eds.): Dermatotoxicology and Pharmacology (3rd. Ed.), Wiley, New York). Any serious lesions or toxic effects other than ocular were recorded. Examinations of the cornea, iris and aqueous humor were facilitated using optical instruments (e.g. hand slit lamp). To define epithelial damage, one drop of a 1% fluorescein solution was

applied to the corneal surface 24 hours after treatment. The eye was then rinsed with normal saline. The eyes were examined under UV light in a darkened room and under diffuse white illumination according to the method of McDonald and Shadduck. This procedure was repeated later if positive effects were noted.

Only effects persisting for more than 24 hours were included in the evaluation. The irritation indices/mean irritation indices were calculated for cornea (opacity), iris, and erythema and swelling (chemosis) of the conjunctivae. The interpretation was based on the individual indices obtained from the two most sensitive animals.

All study-related documentation was archived, in compliance with GLP.

Reliability : (2) valid with restrictions
Guideline study. However, test material purity was not listed.

19.07.2004 (12)

Species : rabbit
Concentration :
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle :
Result : moderately irritating
Classification :
Method :
Year :
GLP :
Test substance :

Source : 3V SIGMA S.p.A. MOZZO (BERGAMO)
3V Sigma S.p.A. Mozzo Bergamo
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

19.07.2004 (21)

5.3 SENSITIZATION

Remark : Experimental work on sensitization and use tests and patch tests in patients with compounds of the 4,4-diaminostilbenesulfonic acid type revealed no evidence of skin sensitization or local intolerance

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 (disodium salt of CAS No. 81-11-8) published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (11)

5.4 REPEATED DOSE TOXICITY

Type : chronic
Species : rat
Sex : male/female

Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	103 weeks
Frequency of treatm.	:	continuous
Post exposure period	:	none
Doses	:	0, 12500, 25000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	12500 ppm
LOAEL		25000 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)

Remark : The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Methodological information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

The average amount of test material ingested by males from weeks 1-13 in was 765 mg/kg/day for 12500 ppm and 1529 mg/kg/day for 25000 ppm. During weeks 14-104, the average amount of test material ingested by males was 454.5 mg/kg/day for 12500 ppm and 962.5 mg/kg/day for 25000 ppm.

The average amount of test material ingested by females from weeks 1-13 was 841 mg/kg/day for 12500 ppm and 1715 mg/kg/day for 25000 ppm. During weeks 14-104, the average amount of test material ingested by females was 528 mg/kg/day for 12500 ppm and 1085.5 mg/kg/day for 25000 ppm.

The summary in the OECD IUCLID document stated that doses of 12500 and 25000 ppm in the rats were equivalent to 558 and 1151 mg/kg day, respectively. It also stated that “although the animals might have been able to tolerate slightly higher doses, results of the 13 week studies indicate that a doubling of the highest doses could not have been tolerated.”

Result : 15 month examination: “There were no biologically significant absolute or relative organ weight, clinical pathology, or histopathology findings in rats administered disodium 4,4’-diamino-2,2’-stilbene disulfonate in feed for 15 months. “

Body weight, food consumption, survival and clinical findings: “Mean body weights were marginally decreased for high dose male and female rats. Food consumption by dosed rats was similar to food consumption by controls throughout the studies. Survival was similar among control and treated groups of rats. No clinical findings related to chemical administration were observed in rats.”

Non-neoplastic and Neoplastic Effects: “There were no chemical-related increased incidences of neoplasms at any site. Ulcers of the forestomach or glandular stomach occurred in dosed rats (males: 1/10, 5/50, 4/50, females: 0/50, 1/50, 4/50). “

Test condition : Animals: Male and female F344/N rats were observed for 16 days before use. They were approximately 6 weeks old at the beginning of the studies. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 74 degrees F and 50 +/- 15.2 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Cages were rotated weekly. Five animals per sex were randomly

selected and euthanized for parasite evaluation (negative) and gross observation of disease (negative). Groups of 60 rats/sex received feed containing 0, 12500, or 25000 ppm test material for 103 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed at least once every eight weeks to confirm stability.

Study conduct: Animals were observed twice daily and clinical observations were recorded weekly for 13 weeks, then monthly (or as necessary). Animals were weighed at the beginning of the study, weekly for 13 weeks, monthly through week 90, and every 2 weeks thereafter. Food consumption was measured once per month.

After 15 months, 10 animals per sex from each group were euthanized for interim examinations. Blood was withdrawn from the orbital sinus plexus of all surviving animals for hematological (hemoglobin, hematocrit, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total and differential leukocyte counts) and clinical pathology analyses (blood urea nitrogen, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase). The brain, liver and right kidney of each animal were weighed.

Necropsies were performed on all animals. All organs and tissues were examined for gross lesions and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all 15-month interim animals, all tissues with grossly visible lesions, all animals that died or were killed moribund prior to 21 months, and all control and high dose animals that survived to study termination. Tissues examined included the adrenal gland, bone (costochondrial junction), bone marrow (femur), brain, clitoral gland, esophagus, heart, kidney, large intestine, liver, lung, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, preputial gland, prostate, salivary gland, seminal vesicle, skin, small intestine, spleen, stomach, testis (with epididymis), thymus, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined from low dose animals that died or were killed moribund after 21 months or at study termination were gross lesions, adrenal gland, liver (males), kidney (females), mammary gland (females), pituitary gland (males) and spleen (males).

Statistical analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier. The possibility of a dose-

related effect on survival was assessed using the methods of Cox and Tarone. Tumor incidence data were analyzed using a logistic regression analysis which assumed that the tumors were discovered as the result of death from an unrelated cause. The Fisher exact test and the Cochran-Armitage trend test were used to analyze the overall proportion of tumor-bearing animals. Organ and body weight data were analyzed using the multiple comparison procedures of Williams and Dunnett. Clinical chemistry and hematology data were analyzed using the multiple comparison methods of Shirley and Dunn. Jonckheere's test was used to assess the significance of dose-response trends.

Quality check: All slides, blocks and residual tissues were sent to the NTP Archives for inventory, slide/block match and wet-tissue audit. All neoplastic diagnoses from a randomly selected 10% of the control and high dose rats were reevaluated by a different quality assessment pathologist. The NTP Pathology Working Group chair blindly reviewed selected tissues for which there was a disagreement between the laboratory and quality assessment pathologists.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in 27/28 dose formulations were within the acceptable range of +/- 10% of target concentrations at both analyses. The sample that was not within this range was remixed.

Conclusion : There was no evidence of carcinogenic activity in rats receiving 12500 or 50000 ppm test material. However, both doses were associated with slight increases in the incidences of ulceration of the forestomach or glandular stomach of both males and females. Judging from the NOEL assigned to the study, apparently this was not considered to be related to test material administration.

Reliability : (1) valid without restriction
Comparable to a guideline study

Flag : Critical study for SIDS endpoint

(25)

Type : sub-chronic
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 13 weeks
Frequency of treatm. : continuous
Post exposure period : none
Doses : 0, 6250, 12500, 25000, 50000 or 100000 ppm
Control group : yes, concurrent no treatment
NOAEL : 25000 ppm
LOAEL 50000 ppm
Method : other: NTP
Year : 1992
GLP : yes
Test substance : other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)

Remark : The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

According to the OECD summary, a dose of 25000 ppm corresponds to 1207 mg/kg/day in rats.

Result : Mortality: “One female rat receiving 100000 ppm group died during the study.”

Body weight: “Mean body weight gain was significantly decreased in male rats receiving 50000 or 100000 ppm and female rats receiving 100000 ppm.”

Clinical findings: “Clinical findings in male [word “male” omitted in OECD summary] rats receiving 50000 or 100000 ppm or females receiving 100000 ppm were diarrhea, emaciation and hyperemia of the perineum.”

Feed consumption: [these data were not present in the OECD summary] Feed consumption of males in the 100000 ppm group was 35% lower than that of controls during the first week, and remained lower than controls through week 8. Feed consumption of females in the 100000 ppm group was 27% lower than that of controls during the first week. By week 4, feed consumption of females in this group exceeded that of controls.

Organ weights and clinical chemistries: “There were no biologically significant changes in absolute or relative organ weights or clinical pathology results in rats.”

Pathological examination: “Histopathologic lesions present in rats receiving 100000 ppm were bone marrow cellularity and chronic inflammation of the anus and rectum.”

Test condition : Animals: Male and female F344/N rats were observed for 13-15 days before use. They were 6-7 weeks old at the beginning of the studies. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 70.4 degrees F and 43 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Groups of 10 rats/sex received feed containing 0, 6250, 12500, 25000, 50000 or 100000 ppm test material for 13 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed twice during the 13 week study to confirm stability.

Study conduct: Animals were observed twice daily and clinical observations were recorded weekly. Animals were weighed at the beginning of the study and weekly thereafter. Food consumption was measured weekly.

At the end of 13 weeks, rats were anesthetized and blood was withdrawn

from the orbital sinus plexus of all surviving animals for clinical pathology analyses (glucose, total protein, albumin, albumin/globulin ratio, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase). Hematological analyses were not performed.

Necropsies were performed on all study animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. All animals that died or were killed prior to the end of the study, all controls, and all high dose animals received complete histopathologic examinations. The aforementioned tissues plus the adrenal gland, bone and marrow (sternum), cecum, clitoral gland, colon, duodenum, esophagus, ileum, jejunum, left kidney, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, preputial gland, prostate, rectum, salivary gland, spleen, stomach, left testis, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Liver sections from the 0, 25000 and 100000 ppm groups were stained with Oil Red O and periodic acid-Schiff (with and without diastase). The rectum/anus from all groups was examined microscopically.

Statistical analyses: Body weight and absolute and relative (to body weight) organ weight data were analyzed using the Williams' or Dunnett's test. Clinical chemistry data were analyzed using Dunn's or Shirley's test. Incidences of pathological lesions were analyzed using the Fisher exact test. Feed consumption data were not analyzed statistically. The critical level of significance was p <= 0.05.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in the test diets were within the acceptable range of +/- 10% of target concentrations at both analyses.

Reliability : (2) valid with restrictions
Comparable to a guideline study with acceptable restrictions. Hematological analyses were not performed.

Flag : Critical study for SIDS endpoint

(25)

Type	:	sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	14 days
Frequency of treatm.	:	continuous
Post exposure period	:	
Doses	:	0, 6250, 12500, 25000, 50000 and 100000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	= 25000 ppm
LOAEL	:	= 50000 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)

Remark : The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

According to the OECD summary, a dose of 25000 ppm corresponds to 2315 mg/kg/day in rats.

Result : "All rats survived to the end of the study. The mean body weight gains of males receiving 50000 or 100000 ppm and of females receiving 100000 ppm were significantly lower than those of the respective controls. Clinical findings included diarrhea in the rats receiving 100000 ppm. There were no chemical-related changes in absolute or relative organ weights. There were no gross or microscopic lesions related to chemical administration."

Test condition : Animals: Male and female F344/N rats were observed for 15 days prior to exposure. Animals were 6-7 weeks old at study initiation. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 75 degrees F and 55.7 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Groups of 5 rats/sex received feed containing 0, 6250, 12500, 25000, 50000 or 100000 ppm test material for 14 days, followed by a 1 day observation period.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 5 minutes with and 10 minutes without an intensifier bar. Dose formulations were prepared weekly. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed once during the study to confirm stability.

Study conduct: Clinical observations were conducted twice daily. Animals were weighed at the start of the study, and on Days 8 and 16. Food consumption was recorded weekly. Complete necropsies were performed on all animals. The brain, heart, right kidney, liver, lungs and thymus of survivors were weighed at necropsy. All animals in the control and high dose groups received complete histopathologic examinations. Tissues examined included adrenal gland, bone and marrow (sternum), brain, clitoral or preputial gland, colon, esophagus, heart, jejunum, kidney, liver, lung, mammary gland, mandibular lymph node, nasal cavity, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder and uterus.

Statistical analyses: Data were examined using the Williams' or Dunnett's test. The critical level of significance was $p <= 0.05$.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Test material formulations were within 10% of target concentrations.

Reliability : (2) valid with restrictions
Duration of study was less than 28 days

08.07.2004 (25)

Type	:	chronic
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	2 years
Frequency of treatm.	:	daily (feeding study)
Post exposure period	:	no
Doses	:	0, 6250 or 12500 ppm
Control group	:	yes
NOAEL	:	6250 ppm
LOAEL		12500 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)

Remark : The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Methodological information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

The average amount of test material ingested by males from weeks 1-13 was 836 mg/kg/day for 6250 ppm and 1738 mg/kg/day for 12500 ppm. During weeks 14-104, the average amount of test material ingested by males was 763 mg/kg/day for 6250 ppm and 1565 mg/kg/day for 12500 ppm.

The average amount of test material ingested by females from weeks 1-13 was 997 mg/kg/day for 6250 ppm and 2081 mg/kg/day for 12500 ppm. During weeks 14-104, the average amount of test material ingested by females was 666 mg/kg/day for 6250 ppm and 1444 mg/kg/day for 12500 ppm.

The summary in the OECD IUCLID document stated that doses of 6250 and 12500 ppm in the mice were equivalent to 776 and 1656 mg/kg day, respectively. It also stated that “although the animals might have been able to tolerate slightly higher doses, results of the 13 week studies indicate that a doubling of the highest doses could not have been tolerated.”

Result : 15 month examination: “There were no biologically significant absolute or relative organ weight, clinical pathology, or histopathology findings in mice administered disodium 4,4’-diamino-2,2’-stilbene disulfonate in feed for 15 months. “

Body weight, food consumption, survival and clinical findings: “Mean body weights were marginally decreased for high dose female mice. Food consumption by dosed mice was similar to food consumption by the controls throughout the studies. Survival was similar among control and treated groups of mice. No clinical findings related to chemical administration were observed in mice.”

Non-neoplastic and Neoplastic Effects: “There were no chemical-related increased incidences of neoplasm, non-neoplastic lesions, or other toxic effects in mice.”

Test condition : Animals: Male and female B6C3F1 mice were observed for 13 days before use. They were approximately 6 weeks old at the beginning of the studies. Animals were housed 5 per cage initially and allowed free access to food and water. Male mice were housed individually from weeks 39 to termination. Animals were housed under 74 degrees F and 50 +/- 15.2 %

average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Cages were rotated weekly. Five animals per sex were randomly selected and euthanized for parasite evaluation (negative) and gross observation of disease (negative). Groups of 60 mice/sex received feed containing 0, 6250, or 12500 ppm test material for 103 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed at least once every eight weeks to confirm stability.

Study conduct: Animals were observed twice daily and clinical observations were recorded weekly for 13 weeks, then monthly (or as necessary). Animals were weighed at the beginning of the study, weekly for 13 weeks, monthly through week 90, and every 2 weeks thereafter. Food consumption was measured once per month.

After 15 months, 10 animals per sex from each group were euthanized for interim examinations. Blood was withdrawn from the orbital sinus plexus of all surviving animals for hematological (hemoglobin, hematocrit, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total and differential leukocyte counts) and clinical pathology analyses (blood urea nitrogen, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase). The brain, liver and right kidney of each animal were weighed.

Necropsies were performed on all animals. All organs and tissues were examined for gross lesions and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all 15-month interim animals, all tissues with grossly visible lesions, all animals that died or were killed moribund prior to 21 months, and all control and high dose animals that survived to study termination. Tissues examined included the adrenal gland, bone (costochondrial junction), bone marrow (femur), brain, esophagus, gallbladder, heart, kidney, large intestine, liver, lung, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, prostate, salivary gland, seminal vesicle, skin, small intestine, spleen, stomach, testis (with epididymis), thymus, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined from low dose animals that died or were killed moribund after 21 months or at study termination were gross lesions, liver (males) and lung.

Statistical analyses: The probability of survival was estimated by the

product-limit procedure of Kaplan and Meier. The possibility of a dose-related effect on survival was assessed using the methods of Cox and Tarone. Tumor incidence data were analyzed using a logistic regression analysis which assumed that the tumors were discovered as the result of death from an unrelated cause. The Fisher exact test and the Cochran-Armitage trend test were used to analyze the overall proportion of tumor-bearing animals. Organ and body weight data were analyzed using the multiple comparison procedures of Williams and Dunnett. Clinical chemistry and hematology data were analyzed using the multiple comparison methods of Shirley and Dunn. Jonckheere's test was used to assess the significance of dose-response trends.

Quality check: All slides, blocks and residual tissues were sent to the NTP Archives for inventory, slide/block match and wet-tissue audit. All neoplastic diagnoses from a randomly selected 10% of the control and high dose rats were reevaluated by a different quality assessment pathologist. The NTP Pathology Working Group chair blindly reviewed selected tissues for which there was a disagreement between the laboratory and quality assessment pathologists.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in 27/28 dose formulations were within the acceptable range of +/- 10% of target concentrations at both analyses. The sample that was not within this range was remixed.

Reliability : (1) valid without restriction
Comparable to a guideline study

Flag : Critical study for SIDS endpoint

(25)

Type : sub-chronic
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 13 weeks
Frequency of treatm. : continuous
Post exposure period : none
Doses : 0, 6250, 12500, 25000, 50000 or 100000 ppm
Control group : yes, concurrent no treatment
NOAEL : 12500 ppm
LOAEL 25000 ppm
Method : other: NTP
Year : 1992
GLP : yes
Test substance : other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)

Remark : The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

According to the OECD summary, a dose of 12500 ppm corresponds to 1681 mg/kg/day in mice.

Although the summary included in the dossier for CAS No. 81-11-8 presented at SIAM 4 indicated that female mice in the 6250, 12500 and 50000 ppm dose groups had increased incidences of cystic endometrial

hyperplasia, the NOEL was reported as 12500 ppm. As reported in the study documentation, there was a significant increase in the incidence of cystic endometrial hyperplasia in females receiving the 25000 ppm dose (5/10 vs. 0/10 in control). This did not appear to be related to treatment, since the incidence did not increase with dose. Additional findings that were not reported in the SIAM 4 dossier were atrophy of ovaries and the endometrium of the uterus in high dose females and atrophy of the thymus in 5/8 high dose males. Based on these data, the NOAEL of 12500 ppm appears to have been assigned correctly.

Result : Mortality: "Six males and one female receiving 100000 ppm died during the study."

Body weight: "Mean body weight gain was significantly decreased in female mice receiving 50000 or 100000 ppm and male mice receiving 25000, 50000 or 100000 ppm."

Clinical findings: Body tremors, lethargy, emaciation and diarrhea were noted in high dose animals.

Organ weights/clinical chemistry: "There were no biologically significant changes in absolute or relative organ weights or clinical pathology results in mice."

Pathological examination: "Ulcerative inflammation of the anus and rectum was observed in mice receiving 25000 ppm and above. Female mice in the 6250, 12500 and 50000 ppm dose groups had increased incidences of cystic endometrial hyperplasia."

Test condition : Animals: Male and female B6C3F1 mice were observed for 13-15 days before use. They were 7-8 weeks old at the beginning of the studies. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 70.6 degrees F and 43.1 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Groups of 10 mice/sex received feed containing 0, 6250, 12500, 25000, 50000 or 100000 ppm test material for 13 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed twice during the 13 week study to confirm stability.

Study conduct: Animals were observed twice daily and clinical observations were recorded weekly. Animals were weighed at the beginning of the study and weekly thereafter. Food consumption was measured weekly.

At the end of 13 weeks, rats were anesthetized and blood was withdrawn

from the orbital sinus plexus of all surviving animals for clinical pathology analyses (glucose, total protein, albumin, albumin/globulin ratio, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase). Hematological analyses were not performed.

Necropsies were performed on all study animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. All animals that died or were killed prior to the end of the study, all controls, and all high dose animals received complete histopathologic examinations. These aforementioned tissues plus the adrenal gland, anus, bone and marrow (sternum), cecum, colon, duodenum, esophagus, gallbladder, ileum, jejunum, left kidney, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, prostate, rectum, salivary gland, spleen, stomach, left testis, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined in the 6250, 12500, 25000 and 50000 ppm dose groups were the anus, ovary, rectum, uterus and liver. Liver sections from all groups were stained with Oil Red O and periodic acid-Schiff (with and without diastase).

Statistical analyses: Body weight and absolute and relative (to body weight) organ weight data were analyzed using the Williams' or Dunnett's test. Clinical chemistry data were analyzed using Dunn's or Shirley's test. Incidences of pathological lesions were analyzed using the Fisher exact test. Feed consumption data were not analyzed statistically. The critical level of significance was $p <= 0.05$.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in the test diets were within the acceptable range of +/- 10% of target concentrations at both analyses.

Reliability : (2) valid with restrictions
Comparable to a guideline study with acceptable restrictions.
Hematological analyses were not performed.

Flag : Critical study for SIDS endpoint

(25)

Type	:	sub-acute
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	14 days
Frequency of treatm.	:	continuous
Post exposure period	:	
Doses	:	0, 6250, 12500, 25000, 50000 and 100000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	= 25000 ppm
LOAEL	:	= 50000 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)

Remark : The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

According to the OECD summary, a dose of 25000 ppm corresponds to 2618 mg/kg/day in mice.

Result : "All mice survived to the end of the study. The mean body weight gains of males and females receiving 100000 ppm were significantly lower than those of the respective controls. Clinical findings included diarrhea in the mice receiving 100000 ppm. There were no chemical-related changes in absolute or relative organ weights. There were no gross or microscopic lesions related to chemical administration."

Test condition : Animals: Male and female B6C3F1 mice were observed for 16 days prior to exposure. Animals were 7-8 weeks old at study initiation. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 75.6 degrees F and 57.9 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Groups of 5 mice/sex received feed containing 0, 6250, 12500, 25000, 50000 or 100000 ppm test material for 14 days, followed by a 1 day observation period.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 5 minutes with and 10 minutes without an intensifier bar. Dose formulations were prepared weekly. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed once during the study to confirm stability.

Study conduct: Clinical observations were conducted twice daily. Animals were weighed at the start of the study, and on Days 8 and 16. Food consumption was recorded weekly. Complete necropsies were performed on all animals. The brain, heart, right kidney, liver, lungs and thymus of survivors were weighed at necropsy. All animals in the control and high dose groups received complete histopathologic examinations. Tissues examined included adrenal gland, bone and marrow (sternum), brain, colon, esophagus, gallbladder, heart, jejunum, kidney, liver, lung, mammary gland, nasal cavity, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder and uterus. Histopathology of the liver was performed on mice that received 6250, 12500, 25000 or 50000 ppm.

Statistical analyses: Data were examined using the Williams' or Dunnett's test. The critical level of significance was $p <= 0.05$.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Test material formulations were within 10% of target concentrations.

Reliability : (2) valid with restrictions
Duration of study was less than 28 days

08.07.2004 (25)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration	:	up to 5000 micrograms/plate
Cytotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A very brief summary for this study appeared in the OECD dossier presented at SIAM 4. The summary has been expanded to conform to current guidelines.
Result	:	None of the concentrations tested caused an increase in the number of mutants in the absence or presence of 10% rat or hamster liver S-9. All positive controls induced at least a 2-fold increase in the number of mutants with respect to the vehicle control.
Test condition	:	Test material was dissolved in 95% ethanol and incubated with S. typhimurium strains TA98, TA100, TA1535 and TA1537 at 100, 333, 1000, 3333 or 5000 micrograms/ml with or without S-9 from Aroclor 1254-induced rat or hamster liver (10%) for 20 min at 37 degrees C without shaking. Top agar was added and the contents of the tubes were mixed and poured onto the surfaces of petri dishes that contained Vogel-Bonner medium. The colonies present after 2 days of incubation at 37 degrees were hand-counted if there was a precipitate; otherwise automatic colony counters were used. Tests were performed in triplicate. Concurrent solvent and positive controls were run. The positive controls in the absence of S-9 were sodium azide (TA1535 and TA100), 9-aminoacridine (TA97 and TA1537), and 4-nitro-o-phenylenediamine (TA98). The positive control in the presence of S-9 was 2-aminoanthracene for all strains. Concentrations of positive controls were not listed. A chemical was judged to be a mutagen if a dose-related increase over the solvent control was observed and weakly mutagenic if a low-level dose response was seen in duplicate tests. A test was considered questionable if the number of mutants at a single dose was elevated or if an increase that was not dose-related was seen.
Test substance	:	Purity of the test material was 93.7%.
Reliability	:	(2) valid with restrictions Comparable to a guideline study with acceptable restrictions. Four strains were tested instead of 5.
Flag	:	Critical study for SIDS endpoint

08.07.2004 (30)

Type	:	Ames test
System of testing	:	S. typhimurium TA 98, TA 100
Test concentration	:	
Cytotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Mouse liver S-9 mix

Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

06.07.2004 (19)

Type	:	Bacterial reverse mutation assay
System of testing	:	E. coli WP2 uvrA, K12 (343/113)
Test concentration	:	
Cytotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

06.07.2004 (19)

Type	:	Chromosomal aberration test
System of testing	:	Chinese hamster ovary cells
Test concentration	:	up to 1010 micrograms/ml
Cytotoxic concentr.	:	> 1010 micrograms/ml
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1990
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Remark : A summary for this study does not appear in the OECD dossier.

Result : The test for chromosomal aberrations was negative in the absence and presence of S9. In the experiment without S9, the percentage of cells incubated with 101, 303 and 1010 micrograms/ml with aberrations were 3, 1.5 and 2 (compared to 0.5% in control). The positive control mitomycin C (1 and 5 micrograms/ml, respectively) caused 19% and 28% of cells to have aberrations in the absence of S9. In the experiment with S9, the percentage of cells incubated with 101, 303 and 1010 micrograms/ml with aberrations were 1.5, 1.5 and 0 (compared to 2% in control). The positive control cyclophosphamide (50 micrograms/ml) caused 36% of cells to have aberrations in the presence of S9.

Test condition : Chinese hamster ovary (CHO) cells were obtained at their fifth passage level after cloning. Cells were tested regularly for mycoplasma contamination. They were not used beyond the fifteenth passage after cloning. Stocks of CHO cells were maintained at 37 degrees C in McCoy's A (modified) medium buffered with 20 mM HEPES and supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 50 IU/ml penicillin and 50 micrograms/ml streptomycin. Test cultures were set up in 75 cm2 flasks 24 hours before treatment at a density of 1.75 x 10E6 cells/flask.

A stock solution of test material was prepared at 500 mg/ml in water. The chemical was tested as a suspension. A series of dilutions were made from the stock solution to achieve 3 test concentrations in a half-log series (101, 303 and 1010 micrograms/ml). The highest dose used was that which allowed for a sufficient number of cells to be scored at time of harvest.

Chromosomal aberrations in CHO cells were determined by incubating

cells at 37 degrees C (1.75 x 10E6 cells/75 cm2 flask) with test chemical, vehicle or positive control agent (mitomycin C at 1 and 5 micrograms/ml) for 8 hours, washed and treated with colcemid (10-6M) for 2-25 hour before cell harvest. In the experiments with S9, cultures were exposed to the test material, vehicle or positive control (cyclophosphamide at 50 micrograms/ml) in serum-free medium with S9 for 2 hr, washed, and incubated at 37 degrees C for an additional 8 hrs (without S-9). Colcemid was then added, and the cells were harvested 2 hours later. The total durations of the nonactivated and activated experiments were 10 and 12 hrs, respectively. Cells were harvested, stained with Giemsa (5% for 5 min) and scored for aberrations.

All slides (except those from the high dose positive control) were coded and a complete experiment was scored by the same person. Two hundred cells per concentration were scored (with the exception that only 50 cells exposed to 5 micrograms/ml mitomycin C and 50 micrograms/ml cyclophosphamide were scored). Cells were analyzed for the following categories of chromosomal aberrations (simple, complex, and other). Chromatid and chromosome gaps were recorded but not used in the analysis. The frequency of polyploid or endoreduplicated cells was noted only when it seemed excessive. These categories were not included in the totals or statistical analyses.

Simple, complex and other aberrations were combined for the statistical analysis, which was based on the percentage of total cells with aberrations. A binomial sampling assumption was used to examine absolute increases in aberrations over the solvent control at each dose. The P values were adjusted by Dunnett's method to take into account the multiple dose comparisons. A positive result was defined as one for which the adjusted P value was < 0.05. A positive response at a single concentration was designated as having weak evidence for clastogenicity. A test was considered positive if at least two concentrations gave significantly increased responses. A test was repeated to confirm a positive result at one or more concentrations, if toxicity was too great, or if the controls did not give the expected responses.

Test substance : The test material was obtained from ICN K and K Laboratories. Purity was 93.7%.

Reliability : (1) valid without restriction
Comparable to a guideline study.

Flag : Critical study for SIDS endpoint

07.07.2004 (15)

Type : Sister chromatid exchange assay
System of testing : Chinese hamster ovary cells
Test concentration : up to 1020 micrograms/ml
Cytotoxic concentr. : > 1020 micrograms/ml
Metabolic activation : with and without
Result : negative
Method : other
Year : 1990
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : A summary for this study does not appear in the OECD dossier.
Result : The test for sister chromatid exchange (SCE) was negative in the absence and presence of S9. The highest value was 6.86 SCE/cell at 102 micrograms/ml (compared to 6.6 SCE/cell in the vehicle control) in the absence of S9 and 7.18 SCE/cell at 306 micrograms/ml (compared to 6.92 SCE/cell in the vehicle control) in the presence of S9. The positive control mitomycin C induced 8.96 and 20.1 SCE per cell at 0.0015 and 0.01 micrograms/ml (respectively) in the absence of S9. The positive control

cyclophosphamide induced 11.22 and 32.4 SCE per cell at 0.5 and 2.5 micrograms/ml (respectively) in the presence of S9.

Test condition : Chinese hamster ovary (CHO) cells were obtained at their fifth passage level after cloning. Cells were tested regularly for mycoplasma contamination. They were not used beyond the fifteenth passage after cloning. Stocks of CHO cells were maintained at 37 degrees C in McCoy's A (modified) medium buffered with 20 mM HEPES and supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 50 IU/ml penicillin and 50 micrograms/ml streptomycin. Test cultures were set up in 75 cm2 flasks 24 hours before treatment at a density of 1.25 x 10E6 cells/flask.

A stock solution of test material was prepared at 500 mg/ml in water. The chemical was tested as a suspension. A series of dilutions were made from the stock solution to achieve 3 test concentrations in a half-log series (102, 306 and 1020 micrograms/ml). The highest dose used was that which allowed for a sufficient number of cells to be scored at time of harvest.

Cells were exposed to test material, vehicle, or positive control agent (mitomycin C at 0.0015 and 0.01 micrograms/ml without S-9 and cyclophosphamide 0.5 and 2.5 micrograms/ml with S-9) in the absence or presence of S-9 for 2 hours before addition of bromodeoxyuridine (BrDU; 10E-5 M). In cells that were incubated with S-9, test medium did not contain serum. Flasks were sealed. Cultures were incubated for 24 additional hours with BrDU. The chemical and BrDU were then removed and cells were rinsed twice with PBS. Fresh medium with BrdU and colcemid were added and the cells were incubated at 37 degrees C for an additional 2-2.5 hr. Cells were then examined for toxicity (% confluency of monolayer). Cells were then harvested, treated for 12 min at 37 degrees C with hypotonic buffer, and resuspended in 3 volumes of fixative. Slides were prepared and examined with fluorescence microscopy to determine the frequency of metaphase cells that had completed one or two cell cycles in BrDU (M1 or M2 cells). Fifty second division M2 cells from each of the top 3 test concentrations were scored for SCEs.

All slides (except those from the high dose positive control) were coded and a complete experiment was scored by the same person. A trend test of SCEs per chromosome vs. log of concentration was used to examine data. A 20% increase in sister chromatid exchange at 2 doses was considered positive.

Test substance : The test material was obtained from ICN K and K Laboratories. Purity was 93.7%.

Reliability : (1) valid without restriction
Comparable to a guideline study.

07.07.2004 (15)

Type : Bacterial reverse mutation assay
System of testing : S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration : 100 – 5000 micrograms/plate
Cytotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method :
Year : 1992
GLP : yes
Test substance : other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)

Test condition : With and without Aroclor 1254-induced male SD rat or Syrian hamster liver S9 mix
Source : SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability : (2) valid with restrictions
Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted

at SIAM 4 and posted on the OECD website.

07.07.2004 (25)

Type	:	Cytogenetic assay
System of testing	:	Chinese Hamster CHO cells
Test concentration	:	
Cytotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	
Year	:	1992
GLP	:	yes
Test substance	:	other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)
Test condition	:	With and without Aroclor 1254-induced male SD rat liver S9 at concentrations up to 1020 micrograms/ml or 5000 micrograms/ml
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

07.07.2004 (25)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

Type	:	chronic
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	103 weeks
Frequency of treatm.	:	continuous
Post exposure period	:	none
Doses	:	0, 12500, 25000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	25000 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)

Remark : The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added.

Additional information about this study is present in Section 5.4. The NOAEL listed above is for carcinogenicity. The NOAEL for repeated dose toxicity is listed in Section 5.4.

The average amount of test material ingested by males from weeks 1-13 in was 765 mg/kg/day for 12500 ppm and 1529 mg/kg/day for 25000 ppm. During weeks 14-104, the average amount of test material ingested by males was 454.5 mg/kg/day for 12500 ppm and 962.5 mg/kg/day for 25000 ppm.

The average amount of test material ingested by females from weeks 1-13 was 841 mg/kg/day for 12500 ppm and 1715 mg/kg/day for 25000 ppm. During weeks 14-104, the average amount of test material ingested by females was 528 mg/kg/day for 12500 ppm and 1085.5 mg/kg/day for 25000 ppm.

The summary in the OECD IUCLID document stated that doses of 12500 and 25000 ppm in the rats were equivalent to 558 and 1151 mg/kg day, respectively.

The marginally increased incidence of malignant pheochromocytoma in high dose male rats was not considered to be related to test material since there was no concomitant increase in the incidence of adrenal medullary hyperplasia, benign pheochromocytomas or benign or malignant pheochromocytomas combined, the incidences of malignant pheochromocytomas in the low and high dose males were within the NTP historical group range of 10-20%, and there was no clear biological distinction between adrenal medullary neoplasms diagnosed as benign or malignant.

The incidence of fibroadenomas in the controls was below the mean for NTP historical controls (39.3%) and the incidences in the dosed groups (42%) were only slightly greater than the historical controls and were within the range of historical controls (8-58%). Therefore, the increased incidences of this lesion were not considered to be related to test material.

Result : 15 month interim examination: There were no significant differences in histopathologic observations between controls and treated animals.

Pathological examination at study termination: There was a significant positive trend for malignant pheochromocytoma of the adrenal medulla in dosed males (4%, 8% and 16% in 0, 125000 and 25000 ppm groups). One malignant pheochromocytoma in a high dose male metastasized. A positive trend was not seen for benign pheochromocytomas or for benign or malignant pheochromocytomas combined. There was no corresponding dose-related increased incidence of adrenal medulllary hyperplasia (17/48, 21/50 and 13/50 in 0, 125000 and 25000 ppm groups).

The incidences of fibroadenomas in the low and high dose female rats were significantly increased relative to controls (21/50, 21/50 and 11/50, respectively).

Test condition : Animals: Male and female F344/N rats were observed for 16 days before use. They were approximately 6 weeks old at the beginning of the studies. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 74 degrees F and 50 +/- 15.2 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Cages were rotated weekly. Five animals per sex were randomly selected and euthanized for parasite evaluation (negative) and gross observation of disease (negative). Groups of 60 rats/sex received feed containing 0, 12500, or 25000 ppm test material for 103 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the

samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed at least once every eight weeks to confirm stability.

Study conduct: Necropsies were performed on all interim (terminated at 15 weeks) and main study animals. All organs and tissues were examined for gross lesions and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all 15-month interim animals, all tissues with grossly visible lesions, all animals that died or were killed moribund prior to 21 months, and all control and high dose animals that survived to study termination. Tissues examined included the adrenal gland, bone (costochondrial junction), bone marrow (femur), brain, clitoral gland, esophagus, heart, kidney, large intestine, liver, lung, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, preputial gland, prostate, salivary gland, seminal vesicle, skin, small intestine, spleen, stomach, testis (with epididymis), thymus, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined from low dose animals that died or were killed moribund after 21 months or at study termination were gross lesions, adrenal gland, liver (males), kidney (females), mammary gland (females), pituitary gland (males) and spleen (males).

Statistical analyses: Tumor incidence data were analyzed using a logistic regression analysis which assumed that the tumors were discovered as the result of death from an unrelated cause. The Fisher exact test and the Cochran-Armitage trend test were used to analyze the overall proportion of tumor-bearing animals. Jonckheere's test was used to assess the significance of dose-response trends.

Quality check: All slides, blocks and residual tissues were sent to the NTP Archives for inventory, slide/block match and wet-tissue audit. All neoplastic diagnoses from a randomly selected 10% of the control and high dose rats were reevaluated by a different quality assessment pathologist. The NTP Pathology Working Group chair blindly reviewed selected tissues for which there was a disagreement between the laboratory and quality assessment pathologists.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in 27/28 dose formulations were within the acceptable range of +/- 10% of target concentrations at both analyses. The sample that was not within this range was remixed.

Conclusion : "There were no chemical-related increased incidences of neoplasms at any site in rats."

Reliability : (1) valid without restriction
Comparable to a guideline study

(25)

Species	:	rat
Sex	:	male/female
Strain	:	other
Route of admin.	:	oral feed
Exposure period	:	103 weeks
Frequency of treatm.	:	daily
Post exposure period	:	
Doses	:	0, 40, 200 and 100 ppm
Result	:	
Control group	:	yes, concurrent no treatment
Method	:	
Year	:	1975
GLP	:	no data
Test substance	:	

Result : In an investigation of the anti-tumor activities of stilbene derivatives used as brighteners, a marked tumor-inhibiting activity on solid forms of Ehrlich carcinoma, sarcoma 180 and carcinoma 63 was detected. Stilbene derivatives showed no effects on Ehrlich ascites carcinoma.

Source : 3V SIGMA S.p.A. MOZZO (BERGAMO)
3V Sigma S.p.A. Mozzo Bergamo
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
Primary reference was not available. Data came from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

08.07.2004 (22)

Type	:	
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	2 years
Frequency of treatm.	:	daily (feeding study)
Post exposure period	:	no
Doses	:	0, 6250 or 12500 ppm
Control group	:	yes
NOAEL		12500 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	other TS: disodium salt of CAS No. 81-11-8 (CAS No. 7336-20-1)

Remark : The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added.

Additional information about this study is present in Section 5.4. The NOAEL listed above is for carcinogenicity. The NOAEL for repeated dose toxicity is listed in Section 5.4.

The average amount of test material ingested by males from weeks 1-13 was 836 mg/kg/day for 6250 ppm and 1738 mg/kg/day for 12500 ppm. During weeks 14-104, the average amount of test material ingested by males was 763 mg/kg/day for 6250 ppm and 1565 mg/kg/day for 12500 ppm.

The average amount of test material ingested by females from weeks 1-13

was 997 mg/kg/day for 6250 ppm and 2081 mg/kg/day for 12500 ppm. During weeks 14-104, the average amount of test material ingested by females was 666 mg/kg/day for 6250 ppm and 1444 mg/kg/day for 12500 ppm.

The summary in the OECD IUCLID document stated that doses of 6250 and 12500 ppm in the mice were equivalent to 776 and 1656 mg/kg day, respectively.

Result : "There were no chemical-related increased incidences of neoplasms at any site in mice."

Test condition : Animals: Male and female B6C3F1 mice were observed for 13 days before use. They were approximately 6 weeks old at the beginning of the studies. Animals were housed 5 per cage initially and allowed free access to food and water. Male mice were housed individually from weeks 39 to termination. Animals were housed under 74 degrees F and 50 +/- 15.2 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Cages were rotated weekly. Five animals per sex were randomly selected and euthanized for parasite evaluation (negative) and gross observation of disease (negative). Groups of 60 mice/sex received feed containing 0, 6250, or 12500 ppm test material for 103 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed at least once every eight weeks to confirm stability.

Study conduct: Necropsies were performed on all interim (15 week termination) and main study animals. All organs and tissues were examined for gross lesions and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all 15-month interim animals, all tissues with grossly visible lesions, all animals that died or were killed moribund prior to 21 months, and all control and high dose animals that survived to study termination. Tissues examined included the adrenal gland, bone (costochondrial junction), bone marrow (femur), brain, esophagus, gallbladder, heart, kidney, large intestine, liver, lung, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, prostate, salivary gland, seminal vesicle, skin, small intestine, spleen, stomach, testis (with epididymis), thymus, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined from low dose animals that died or were killed moribund after 21 months or at study termination were gross lesions, liver (males) and lung.

Statistical analyses: Tumor incidence data were analyzed using a logistic regression analysis which assumed that the tumors were discovered as the result of death from an unrelated cause. The Fisher exact test and the Cochran-Armitage trend test were used to analyze the overall proportion of tumor-bearing animals. Jonckheere's test was used to assess the significance of dose-response trends.

Quality check: All slides, blocks and residual tissues were sent to the NTP Archives for inventory, slide/block match and wet-tissue audit. All neoplastic diagnoses from a randomly selected 10% of the control and high dose rats were reevaluated by a different quality assessment pathologist. The NTP Pathology Working Group chair blindly reviewed selected tissues for which there was a disagreement between the laboratory and quality assessment pathologists.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in 27/28 dose formulations were within the acceptable range of +/- 10% of target concentrations at both analyses. The sample that was not within this range was remixed.

Reliability : (1) valid without restriction
Comparable to a guideline study

(25)

5.8.1 TOXICITY TO FERTILITY

Type	:	Fertility
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	males: 41 days including 14 days before mating; females: from 14 days before mating to day 3 of lactation
Frequency of treatm.	:	7 days/week
Premating exposure period		
Male	:	14 days
Female	:	14 days
Duration of test	:	
No. of generation studies	:	1
Doses	:	40, 200 or 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL parental	:	= 1000 mg/kg bw
NOAEL F1 offspring	:	= 1000 mg/kg bw
Result	:	negative
Method	:	OECD preliminary reproduction toxicity screening test
Year	:	1995
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The information listed in this summary was published in a JETOC Information Sheet (Special Issue No. 3, No. 32, March 1998).
Result	:	Repeated dose toxicity: The test substance had no effects on clinical signs, body weight changes, food consumption or necropsy findings in either sex. Testicular and epididymal weights were similar among all four groups. No histopathological changes ascribed to the test substance in these reproductive organs were observed in any of the male rats.

Reproductive and developmental toxicity: Parental animals exhibited no effects on reproductive parameters including the copulation index, fertility index, gestation index, delivery index, parturition or maternal behavior. There were no significant differences in the number of offspring or live offspring, sex ratio, live birth index, viability index, or body weight. No abnormal findings attributable to the test substance were noted in external examination, clinical signs or necropsy of the offspring.

Test condition : 0.5% sodium CMC (carboxymethyl cellulose) was used as a vehicle.
The strain of rats was Crj:CD(SD)
Ten animals/sex/group were used in the study.

Source : SIAM 4 SIDS dossier for CAS No. 81-11-8

Test substance : Purity of the test material was 92.02%.

Reliability : (2) valid with restrictions
Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

Flag : Critical study for SIDS endpoint

07.07.2004 (17)

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5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Type : Fertility
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : males: 41 days including 14 days before mating;
females: from 14 days before mating to day 3 of lactation
Frequency of treatm. : 7 days/week
Premating exposure period
Male : 14 days
Female : 14 days
Duration of test :
No. of generation studies : 1
Doses : 40, 200 or 1000 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL parental : = 1000 mg/kg bw
NOAEL F1 offspring : = 1000 mg/kg bw
Result : negative
Method : OECD preliminary reproduction toxicity screening test
Year : 1995
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : This summary is identical to the summary above.

The information listed in this summary was published in a JETOC Information Sheet (Special Issue No. 3, No. 32, March 1998).

Result : Repeated dose toxicity: The test substance had no effects on clinical signs, body weight changes, food consumption or necropsy findings in either sex. Testicular and epididymal weights were similar among all four groups. No histopathological changes ascribed to the test substance in these reproductive organs were observed in any of the male rats.

Reproductive and developmental toxicity: Parental animals exhibited no effects on reproductive parameters including the copulation index, fertility index, gestation index, delivery index, parturition or maternal behavior. There were no significant differences in the number of offspring (total or live), sex ratio, live birth index, viability index, or body weight. No abnormal findings attributable to the test substance were noted in external

examination, clinical signs or necropsy of the offspring.

Test condition : 0.5% sodium CMC (carboxymethyl cellulose) was used as a vehicle.
The strain of rats was Crj:CD(SD)
Ten animals/sex/group were used in the study.

Source : SIAM 4 SIDS dossier for CAS No. 81-11-8

Test substance : Purity of the test material was 92.02%.

Reliability : (2) valid with restrictions
Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

Flag : Critical study for SIDS endpoint

07.07.2004 (17)

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5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Remark : Experimental work on sensitization and use tests and patch tests in patients with compounds of the 4,4-diaminostilbenesulfonic acid type revealed no evidence of skin sensitization or local intolerance

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 (disodium salt) published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (11)

Remark : A summary for this study does not appear in the OECD dossier.

The purpose of the study was to devise an analytical method for detection of workplace concentrations of stilbenes. The only personal sample that contained detectable concentrations of CAS No. 81-11-8 (60 micrograms/m3) was taken from 1/4 operators of a filtration unit. A fixed high volume sampler measured 0.2 to 2 micrograms/m3. The authors concluded that the workers were exposed to low airborne concentrations of the material. The relationship of stilbene exposure to the symptoms experienced by workers (decreased libido and impotence) was not investigated.

Reliability : (4) not assignable
A relationship between exposure to CAS No. 81-11-8 and symptoms of reproductive toxicity was not established. Workers were exposed to chemicals other than stilbene derivatives.

08.07.2004 (9)

5.11 ADDITIONAL REMARKS

Type : other

Remark : A summary for this study does not appear in the OECD dossier.

Ninety-three (72%) of the 129 workers initially identified as potential subjects participated in the study. The study group consisted of 29 males (88%) currently exposed to CAS No. 81-11-8, 23 males who had been

exposed to the material in the past, but were no longer exposed (88%), and 41 males working in an area where plastic additives, but no CAS No. 81-11-8 was produced (59%). Fifteen were excluded (13 based on exposure criteria and 2 based on previous testicular abnormalities prior to employment). Seven workers were added after confirming eligibility. The final study group included 30 current workers (minimum of 30 days immediately previous to study), 20 former workers (currently working in other areas who had worked 30 days or more in the production area) and 35 additives workers.

Demographic characteristics, smoking and drinking habits, work habits, occupational exposures, medical history related to decreased libido such as diabetes, thyroid disease, obesity, use of certain medications, reproductive history and whether the subjects believe that workplace exposures could affect sex drive or fertility were listed on questionnaires. Blood serum was analyzed for total and free testosterone, follicle stimulating hormone (FSH), luteinizing hormone, prolactin and estradiol. The collection of blood samples was shift-standardized. A NIOSH physician blinded to exposure status conducted physical examinations, which consisted of an evaluation of secondary sexual characteristics and external genitalia (including testicular volume).

Least squares regression analysis was used to assess the effect of production of the material on hormone levels. The effect of production on hormone levels also was assessed by multiple logistic regression analysis of the relative odds of falling into the highest or lowest quartiles. Regression modeling proceeded as a modified backwards selection using the results of prior, stratified analyses to assess evidence of confounding and interaction. Age and exposure were retained in all models. Other variables were retained at $p <= 0.1$. Log transformations were used to normalize data for all hormones except the ratio of free:total testosterone, which was normalized with an arcsin transformation. Several demographic, medical, and lifestyle variables were evaluated as potential confounders: age, race, marital status, hourly/salaries status, education, body mass index, variococele, mumps at age 11 or later, fever in the last month, current cold, current use of analgesics, or blood pressure or allergy medication, shift and sleep factors and substance factors (tobacco, caffeine or alcohol use).

The mean ages of the current and former workers and controls were 45.9, 45.2, and 39.0 years, respectively. The ages of the current and former workers were significantly higher than the additives workers ($p < 0.01$). The current workers had worked in the production area significantly longer than the former workers and controls. The numbers of subjects reported ever fathering a pregnancy were similar among groups. The proportion of current and former workers who believed that workplace exposures could cause sexual problems (68.0 and 60.0, respectively) was significantly ($p < 0.01$) greater than in the controls (23.3%). Current and former workers had significantly ($p < 0.05$) lower mean total testosterone concentrations (458 and 442 ng/dl, respectively) than controls (556 ng/dl). Current and former workers were 3.6 and 2.2 times more likely than additives workers to have lowest quartile total testosterone levels (<386 ng/dl) after adjustment for age and body mass index. Duration of employment was inversely correlated with total testosterone concentrations ($p = 0.048$). Average FSH concentrations were lower (but not significantly) in the former in the former workers than in the controls (6.7 vs. 10.3 mIU/ml, $p < 0.06$). The concentrations of the other hormones were similar among groups. The group mean concentrations of all hormones were within clinically normal ranges. There was no difference in testicular volumes between groups. Seven cases of bilateral gynecomastia were found (current workers, N = 2 [8%], former workers, N=3 [23%] and additives workers, n = 2 [8%]). A greater percentage of subjects in the additives control group (14.3%) had

consulted a doctor because of a fertility problem than subjects in the worker (6.7%) or former worker groups (5.0%).

Reliability : (4) not assignable
Sample size was limited. Participation among additives workers was low, and may have skewed results. It is unknown if the additives workers in the study were representative of the whole group. There was no follow-up study.

07.07.2004 (8)

Type : other
Remark : A summary for this study does not appear in the OECD dossier.

This was the second of two reports conducted in response to complaints of sexual dysfunction among males who manufactured CAS No. 81-11-8. The first part of the study is described in the preceding record.

In a cross-sectional design, self-reported sexual function of 30 male workers who manufactured CAS No. 81-11-8 and 20 former workers was compared to that of 35 workers who manufactured plastics additives in a different manufacturing area. Questions to assess potency and libido were excerpted from a 21-item brief Sexual Function Questionnaire of Reynolds et al. (Psychiatry Res. 24:231-250, 1988). Questionnaire items were examined by factor analysis, reducing the data to sexual activity/performance (two factors), interest, satisfaction, and physiologic competence. Stratified analyses were conducted for potentially confounding variables, and adjusted odds ratios were computed. Logistic regression was used to model the association between work in the production area and a low score (< 25^{th} percentile) on each of the factors, controlling for potentially confounding variables. The covariates considered as potential confounders were age, race, marital status, employment status (hourly/salaried), body mass index, tobacco use, alcohol consumption, current use of medications, other exposures outside of work, history of diabetes, mumps at age 11 or later, neurologic problems, and sleep characteristics.

To examine the link between reported symptoms of libido/potency and levels of testosterone, two-way analysis of variance was used to calculate adjusted least squares mean hormone levels for each combination of exposure and dichotomized libido/potency factor. The scores were separated into those falling below the 25^{th} percentile for that factor, and those scores falling into the upper three quartiles.

Adjusting for age, current workers were more likely than unexposed workers to have a value in the lowest quartile for interest (adjusted odds ratio = 1.9), physiologic competence (adjusted odds ratio = 1.9) and activity performance factor II (adjusted odds ratio = 5.8). Former workers reported problems associated with activity/performance factors I (quality of erection, pleasure, length of intercourse, ejaculation without full erection) and II (frequency of sex drive, frequency of sexual thoughts, frequency of sexual activities and response to partner's sexual advances) compared to unexposed workers (adjusted odds ratios = 2.2 and 6.7, respectively). There was no clear relationship between testosterone level and reported symptoms of low/libido potency (lowest quartile vs. all other quartiles).

Reliability : (4) not assignable
Selection bias may have occurred if workers with symptoms were more likely to participate than those without symptoms. Sample size was limited. Participation among additives workers was low, and may have skewed results. It is unknown if the additives workers in the study were representative of the whole group. Outcome measures were of a subjective nature. There was no follow-up study.

08.07.2004 (27)

Type : other
Remark : A summary for this study does not appear in the OECD dossier.

Men employed in a large chemical plant that manufactured CAS No. 81-11-8 reported problems with impotence. Although manufacturing processes largely were automated, potential worker exposures to chemicals occurred at reactor charging ports, transfer points, sampling ports, and in filtering and drumming operations. The study population consisted of 44 men aged 20-57 years (mean age 37) employed at the time of the evaluation. An industrial hygiene investigation and health and work history questionnaire survey were conducted. The questionnaire included an assessment of other factors involved in impotence such as diabetes mellitus, thyrotoxicosis, obesity, alcohol ingestion, antihypertensive, amphetamine, marijuana or cocaine use, serious physical or psychological stress, and genitourinary, endocrine, cardiovascular or neurologic disease. A smoking history also was taken. Blood samples were taken for CBC and serum biochemistry (total protein, albumin, bilirubin, alkaline phosphatase, SGOT, testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin, and thyroxin). The first set of samples was drawn at various times of day throughout each work shift and a second set was drawn at a standardized time. Physical examinations were performed, which consisted of an evaluation of secondary sexual characteristics, genitalia and the peripheral nervous system including the bulbocavernosus reflux.

Fourteen percent of the men reported symptoms of impotence over the preceding 6 or more months (defined as a 25% or greater failure rate in obtaining or sustaining penile erection), 7% had potency problems of shorter duration, and 7% were not currently impotent but had experienced impotence for 6 or more months in the past. Thirty six percent experienced decreased libido (desire for sexual relations leading to a 25% or greater decline in sexual relations during the 2 years prior to the study) since beginning work in the production area.

Low levels of serum testosterone (<350 ng/dl, the lower limit of normal) were observed in 37% of the men. However, there was no difference in the testosterone levels between those reporting current impotence [407 +/- 109 ng/dl (n=6)] and those with no impotence [457 +/- 178 ng/dl (n = 37)]. The slope of the regression of serum testosterone level and duration of work (-12.0 ng/dl/year) was not significant (p = .14). Levels of other hormones were generally within the normal ranges. Physical examinations showed no abnormalities of external genitalia. There was no evidence of feminization.

Nineteen personal samples and one high-volume area sample were analyzed for CAS No. 81-11-8 and intermediates used in its production (para-nitrotoluene sulfonic acid and 4,4'-dinitrostilbene-2,2'-disulfonic acid). One personal sample had a detectable amount of CAS No. 81-11-8 (detection limit approximately 20 micrograms/m3). This sample was from the operator of a filter press. The testosterone concentration of this individual was not stated. Thirty eight percent of the samples had detectable levels of 4,4'-dinitrostilbene-2,2'-disulfonic acid, and 24% had detectable levels of para-nitrotoluene sulfonic acid. The relationship of exposure to these materials and incidences of impotence (or levels of testosterone) was not examined.

Reliability : (4) not assignable
The study size was small. An additional group that was not exposed to the material also should have been included. The self-reporting of impotence may be subject to reporting bias. There was no significant correlation between testosterone level and duration of work in the production area. Levels of CAS No. 81-11-8 were undetectable in all but one instance. There was no follow up study.

08.07.2004 (20)

Type : other
Remark : A summary for this study does not appear in the OECD dossier.
Result : The relative uterine weights for animals injected intraperitoneally were as follows:

Dose (mg/kg)	Test material (N)	Control (N)
0.1	1.20 +/- 0.14 (5)	1.22 +/- 0.11 (5)
1	1.27 +/- 0.11 (5)	1.22 +/- 0.11 (5)
10	1.05 +/- 0.27 (15)	0.95 +/- 0.23 (14)
30	0.93 +/- 0.06 (8)	0.80 +/- 0.11 (9)
100	1.04 +/- 0.18 (15)	0.94 +/- 0.23 (15)
300	1.13 +/- 0.19 (25)*	0.68 +/- 0.14 (24)
1000	1.41 +/- 0.31 (15)*	0.94 +/- 0.23 (15)

* Significantly different from control, $p < 0.001$.

There were no overt signs of toxicity or changes in body weight in animals treated intraperitoneally with up to 1000 mg/kg.

Uterine weights of animals given single oral doses of 1000 or 3000 mg/kg were approximately 50% and 90% higher than controls. Overt signs of toxicity were not observed.

Test condition : Female, Sprague Dawley rats had free access to food and water. Groups of 5-25 animals were injected intraperitoneally with 0.1, 1, 10, 30, 100, 300 or 1000 mg/kg test material (or 10 ml/kg saline vehicle) or administered the same doses by oral gavage using a fixed volume of 10 or 30 ml/kg. Signs of toxicity, initial and final body weight and uterine weights were calculated 24 hours after dosing. Data were analyzed using multiple, independent t-tests. The calculated p values were subjected to a Bonferroni adjustment for additive type 1 error due to multiple comparisons.
Reliability : (4) not assignable
The evaluation of the i.p. results are limited by the wide range of mean control values of 0.68 to 1.22 by comparison with the mean values for the free acid of 0.93 to 1.41. The values at 300 and 1000 mg/kg may have been different than controls because at these doses, the control values were lower than for other groups. The variability with the control uterine weights in the i.p. study questions the validity of the results of the oral study.

08.07.2004 (23)

Type : other
Remark : The free acid (CAS No. 81-11-8) showed in vitro some effect as a chloride channel blocker.
Source : Bayer AG Leverkusen
Reliability : (4) not assignable
The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 (disodium salt) published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (26)

Remark : Human erythrocytes in vitro: inhibition of sulfate anion permeability.
Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable
Primary reference was not available. Data came from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

07.07.2004 (5)

Remark	:	It is predicted of the outcome of rodent carcinogenicity bioassays currently conducted by the NTP that 81-11-8 is not carcinogenic in rats or mice.
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data came from an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

07.07.2004 (24)

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

201-16114

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I U C L I D

Data Set

Existing Chemical	:	ID: 78447-91-3
CAS No.	:	78447-91-3
Chemical Name	:	Benzenesulfonic Acid, 2, 2'-(1,2-Ethenediyl)bis(5-nitro)-, Dipotassium salt
Common Name	:	2,2'-Stilbendisulfonic acid-4,4'-dinitro, dipotassium salt
Molecular Weight	:	506.6
Molecular Formula	:	C14H10N2O10S2 x (K)2

Producer related part

Company	:	PCA Services, Inc
Creation date	:	07.07.2004

Substance related part

Company	:	PCA Services, Inc
Creation date	:	07.07.2004
Status	:	
Memo	:	
Printing date	:	30.06.05
Revision date	:	30.06.05
Date of last update	:	30.06.05
Number of pages	:	24
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

Remark: This chemical is the potassium salt of CAS No. 3709-43-1, which is the sodium salt (and a category member).

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

4,4'-Dinitro-2,2'-stilbenedisulfonic acid, dipotassium salt

2,2’-Stilbenedisulfonic acid-4,4’-dinitro, dipotassium salt

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	> 200 °C
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Since the substance is a salt, it will have a high melting point as is consistent with other members of the category.
Reliability	:	(4) not assignable

(4)

Value		349.84 °C
Decomposition		
Method		other: calculation using EPIWIN MPBPWIN (v1.41)
Year		2005
GLP		no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Since the substance is a salt, it will have a melting point above 300 degrees C, as is consistent with other members of the category. The material is included in the category only to provide supplemental information. The model was run on this material to show that its melting point is similar to that of CAS No. 3709-43-1, which is a similar material.
Test condition	:	CAS No 78447-91-3 was inputted into the model.
Reliability	:	(2) valid with restrictions Data were obtained by model estimation.

2.2 BOILING POINT

Remark	:	No data available. Since the substance is a salt, a boiling point is irrelevant for this material.

2.3 DENSITY

Type	:	bulk density
Value	:	= 650 kg/m3 at 20 °C
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 78447-91-3 published by Bayer AG on 06.11.2003 and updated on 08.09.2003.

(4)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Remark	:	No data available. Since the substance is a salt, and does not exist as a neutral molecule, it cannot exist in vapor form or exert a meaningful vapor pressure.

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	-2.52

pH value	:	
Method	:	other: calculated using EPIWIN KOWWIN (v1.67) Model, inputting the SMILES code for CAS No. 78447-91-3
Year	:	2005
GLP	:	
Test substance	:	as prescribed for 1.1 -1.4
Remark	:	The material is included in the category only to provide supplemental information. The model was run on this material to show that its log Pow is similar to that of CAS No. 3709-43-1, which is a similar material.
Reliability	:	(2) valid with restrictions. Value was obtained by modeling.
Partition coefficient	:	
Log pow	:	= .2 at °C
pH value	:	
Method	:	other (calculated): Leo, A: CLOGP-3.54 Med Chem Software 1989. Daylight, Chemical Information Systems, Claremont CA 91711
Year	:	
GLP	:	
Test substance	:	
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 78447-91-3 published by Bayer AG on 06.11.2003 and updated on 08.09.2003.

(5)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	water
Value	:	= 4.34 g/l at 20 °C
pH value	:	= 7.3
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	
Description	:	
Stable	:	yes
Deg. product	:	
Method	:	other: Flask method using internal Bayer SOP
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A water solubility of 3.69 g/l was given for the acid form of the molecule, which has a molecular weight of 430.3. The water solubility of the dipotassium salt, with a molecular weight of 506.6 is calculated to be 4.34 g/l based on the water solubility of the acid.
Test condition	:	Additional details about the test conditions were not listed. Purity of the material was not mentioned.
Reliability	:	(2) valid with restrictions Although the study was conducted per a standard procedure, and following GLP, details of the study or SOP were not given.
Flag	:	Critical study for SIDS endpoint

14.06.2005 (3)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Remark	:	This material does not volatilize to any degree, since it is an ionized, organic salt. Therefore, it will not be found in any significant concentration in the atmosphere other than in particle form. For this reason, atmospheric photodegradation is not an appreciable or important degradative pathway.
Reliability	:	(2) valid with restrictions. Information is based on chemical structure.

3.1.2 STABILITY IN WATER

Remark	:	No data available. The substance does not contain any functional groups subject to hydrolysis, and should be stable in water.

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other: air, water, soil, biota
Air	:	5.27 E-26 % (Fugacity Model Level III)
Water	:	59.1 % (Fugacity Model Level III)
Soil	:	% (Fugacity Model Level I)
Biota	:	.112 % (Fugacity Model Level II/III)
Soil	:	40.8 % (Fugacity Model Level II/III)
Method	:	other: calculation using EPIWIN v3.11
Year	:	2005
Remark	:	The material is included in the category only to provide supplemental information. The model was run on this material to show that its environmental fate is similar to that of CAS No. 3709-43-1, which is a similar material.
Result	:	Half-lives in various media are air:1.47 hours; water: 1440 hours; soil: 1440 hours; and sediment: 5760 hours. The soil-sediment coefficient [calculated by EPIWIN PCKOC (v1.66)] is Koc = 1.47.E+4.
Test condition	:	Inputs to the model are the SMILES code for CAS No. 78447-91-3 and emission rates: air: 0 kg/hr, water: 1000 kg/hr, and soil: 1000 kg/hr.
Reliability	:	(2) valid with restrictions Data were obtained by modeling.

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	
Concentration	:	250 mg/l related to DOC (Dissolved Organic Carbon) 20 mg/l related to COD (Chemical Oxygen Demand)
Contact time	:	
Degradation	:	= .7 (±) % after 29 day(s)
Result	:	under test conditions no biodegradation observed
Control substance	:	Aniline
Kinetic	:	7 day(s) = 100 % %
Deg. product	:	
Method	:	other: Modified OECD Screening Test
Year	:	1989
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Date of solutions prep.: March 4, 1989 Stock Solution: 1.0 g/l Inoculum: 10 liters (type of sludge not mentioned) There was no information about temperature or test material purity.
Reliability	:	(2) valid with restrictions Basic data given.
Flag	:	Critical study for SIDS endpoint

26.07.2004 (6)

Type	:	
Inoculum	:	predominantly domestic sewage
Concentration	:	20 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	
Degradation	:	= 0 (±) % after 29 day(s)
Result	:	under test conditions no biodegradation observed
Deg. product	:	
Method	:	OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year	:	
GLP	:	
Test substance	:	
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 78447-91-3 published by Bayer AG on 06.11.2003 and updated on 08.09.2003.

22.07.2004 (4)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	= 3395
LC50	:	> 3395
Limit test	:	no
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : The test substance was only partially dissolved (soluble), with a dark brown sediment. Also, all concentrations had a brown sediment. Increasing coloration of the medium was observed with increasing concentrations from light gold (at 10 mg/l) to deep orange (10 g/l). Since measured concentrations were considerably less than nominal, the results are expressed in terms of measured (rather than nominal) concentrations.

Result : None of the fish died and no toxicity was observed. The LC0 = 10,000 mg/l (nominal).

The range of oxygen concentrations over the course of the study was 7.46-7.67 mg/l (lowest) to 8.44-8.68 (highest). The average was 7.95-8.09 for the various concentrations. The standard deviation was 0.36-0.59 mg/l.

The pH range for all concentrations and times was 7.72-7.91 (lowest) to 7.81-7.97 (highest). The average was 7.79-7.93 for the various concentrations. The standard deviation was 0.02-0.08 mg/l.

Analytical measurements made throughout the study were in rough agreement with the nominal concentration but were generally less. The average concentrations measured were 0.677, 5.69, 61.2, 644, and 3395 mg/l compared to 1, 10, 100, 1000, and 10,000 nominal.

Test condition : Test organism: The species was zebra fish. The fish came from a German Breeder (Doller Zierfisch). The fish arrived in good health and without noticeable deformities. The fish were kept under a light/dark cycle of 14/10 hours. Average weight of the fish was 188 mg (Series 1) and 164 mg (Series 2). Average length was 3.1 cm (Series 1) and 3.0 cm (Series 2).

Dilution Water: Dilution water was prepared according to the test guideline and an internal SOP. The pH and oxygen concentration at the beginning of the test were 7.84 and 7.98 mg/l, respectively.

Preparation of test concentrations: The test material was stored at room temperature in the closed original container. The two highest concentrations (1.0 and 10.0 g/l) were directly weighed into the end volume. For the other concentrations, stock solutions in dilution water (100 mg/l) were prepared. Aliquots of the stock solution were stirred vigorously with a magnetic stirrer when diluted to the test concentrations. Concentrations tested were 0 (control), 1.0, 10, 100, 1,000 and 10,000 mg/l.

Test conduct: Ten fish were employed per test concentration. Food was removed 24 hours before the test. Fifteen-liter completely glass aquariums were filled with 5.0 liter test solution and held at 23 +/-1 degrees. Controls

were treated in the same manner. Concentrations of test material were measured at 0, 45 and 96 hours. The pH and the oxygen concentrations of the control and test media were determined right before adding the test fish and after 24, 48, and 96 hours. Mortality was determined after 24, 48, 72 and 96 hours and any observations were recorded. Dead animals were removed from the container as soon as discovered. The criteria for mortality were those of the OECD guidelines.

Test substance : The test material contained 64.4% CAS No. 78447-91-3 and 24.6% water.

Reliability : (2) valid with restrictions
OECD Guideline study. The study was in German, and pertinent sections were translated to prepare this summary.

Flag : Critical study for SIDS endpoint

09.08.2004 (8)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Remark : No data available. Endpoint does not need to be filled for this material, which is only included in the category to provide supplemental information.

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Remark : No data available. Endpoint does not need to be filled for this material, which is only included in the category to provide supplemental information.

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type :
Species : activated sludge
Exposure period : 3 hour(s)
Unit : mg/l
EC50 : > 10000
Method : other: Test for inhibition of oxygen consumption by activated sludge, ISO 8192
Year : 1989
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : There was 59% inhibition of oxygen consumption of the sludge at 20.0 mg/l reference substance.

Test condition : Test: Bacteria toxicity and Oxygen consumption test with activated sludge
Study date: Feb 21, 1989
Reference substance: 3,5-dichlorophenol (1.0 and 20.0 mg/l)
Inoculant: 3L laboratory material (OECD)
Initial concentration of industrial sludge: 6.00 g/l
Nutrient medium: Prepared according to ISO 8192-1986
Test material concentrations: 100, 1000 and 10000 mg/l.
Temperature: 20.3-21.7 degrees C
p: 7.9 to 8.2

Reliability : (2) valid with restrictions
Basic data given. Purity of the test material was not stated. The study was in German, and pertinent sections were translated to prepare this summary.

26.07.2004 (7)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	water
Doses	:	2000 mg/kg
Method	:	Directive 84/449/EEC, B.1 "Acute toxicity (oral)"
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No deaths and no symptoms of toxicity.
Result	:	The LD50 was found to be >2000 mg/kg bw for male and female rats and was not exactly determined. No animals died during the 14-day post observation period. Symptoms of poisoning were not observed. The growth and development of the rats were not influenced. All of the animals that were euthanized at the end of the 14-day observation period were examined pathologically and anatomically, with no remarkable findings.
Test condition	:	Experimental Animals: Young adult SPF bred Wistar-rats (Stam Bor: WISW (SPF Cpb), Breeder: Winkelmann, Borchen) were used in the study. At the beginning of the study the rats were about 8 (male) and 9 (female) weeks old, corresponding to their weight. The male animals had an average beginning weight of 186 g and the female animals an average weight of 156 g. The variation in weight was less than 20% of the average weight. The females were virgins. The animals were examined before the beginning of the study and ascertained to be healthy and symptom free. The animals were adapted for at least 5 days before use. Five rats per sex were employed. The rats were held in conventional cages in groups of 5 on particle wood grain bedding at a room temperature of 22 +/-2 degrees C, with a 12 hour light/dark cycle. Relative humidity was about 50 +/- 10%. There were 10 air exchanges per hour. Animals were allowed free access to food and water, with the exception that the animal feed was taken away from 16 hours before dosing until 4 hours after dosing. Test material: The test material was suspended at room temperature in distilled water at approximately 200 g/l and stirred magnetically. The suspension of the test substance in water was homogenous. The stability of the test dose was confirmed analytically. Study conduct: The test material (2000 mg/kg bw) was administered by gavage at constant dose volume of 10 ml/kg bw to each of the 5 male and female animals. The animals were examined on the day of the application (Day 0) and 2 times per day for 14 days (except only one time per day on weekends and holidays). Dead animals were removed promptly. The animals were individually weighed before the dosing (Day 0), after a week and at the end of the 14-day observation time. The animals were euthanized with diethyl ether 14 days after treatment and were pathologically and anatomically examined. All animals were autopsied per protocol.

Test substance	:	Test substance content was about 74.3% (64.4% organic part plus 9.91 % potassium ion). Physical state and appearance of test material was solid, gold crystals. The melting point was >200 degrees C. The pH of a 100 g/l solution in water was 7.
Reliability	:	(1) valid without restriction Guideline study.
Flag	:	Critical study for SIDS endpoint

26.07.2004 (2)

Type	:	
Value	:	= 12000 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: 4,4'-Dinitro-2,2'-stilbenedisulfonic acid

Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 78447-91-3 published by Bayer AG on 06.11.2003 and updated on 08.09.2003.

(10)

Type	:	LD50
Value	:	= 47000 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: 4,4'-Dinitro-2,2'-stilbenedisulfonic acid

Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 78447-91-3 published by Bayer AG on 06.11.2003 and updated on 08.09.2003.

(11)

Type	:	LD50
Value	:	= 30000 mg/kg bw
Species	:	rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: 4,4'-Dinitro-2,2'-stilbenedisulfonic acid

Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID

document for CAS No. 78447-91-3 published by Bayer AG on 06.11.2003 and updated on 08.09.2003.

(11)

Type	:	LD50
Value	:	= 71000 mg/kg bw
Species	:	guinea pig
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: 4,4'-Dinitro-2,2'-stilbenedisulfonic acid
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 78447-91-3 published by Bayer AG on 06.11.2003 and updated on 08.09.2003.

(11)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	500 mg
Exposure	:	
Exposure time	:	4 hour(s)
Number of animals	:	3
Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other: OECD Guideline 404
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	There were no departures from the guidelines that would have influenced either the validity or the interpretation of the results of these studies. The study was translated from German to English.
Result	:	Scoring was negative for erythema and crust formation or edema formation. All scores were zero. The test substance was not irritating or corrosive to skin.
Test condition	:	Time period of the study: Jan. 31 to Feb. 7, 1989 Test substance: The stability of the test substance was guaranteed over

the duration of the study. It was stored at room temperature in absence of light. It was a gold powder. The pH of a 100 g/l solution was 7.

Animals: All animals were healthy adult, female albino rabbits of the strain HC:NZW (breeder: Interfauna UK Ltd.). The animals had never been mated. The rabbits were kept under standard conditions in single cages and allowed free access to standard rabbit chow and water. Animals were identified using ear tags and by their cages. The rabbits were quarantined for at least 14 days before the study. Shortly after arrival, they were examined collectively for Coccidien Oocysten. After the adaptation phase all animals were examined one day before the study to assure they were healthy. Only healthy symptom free animals were used. There was no vaccination or treatment with anti-infective agents. Room conditions were 20 +/-3 degrees C, 50% relative humidity, 12/12 hour light/dark cycle, and 10 air changes/hr. The three rabbits weighed 3.4, 3.2, and 3.4 kg.

Study conduct: The animals were weighed on the first day of the study immediately before exposure. The contralateral skin section (6x6 cm) of the flank on each of 3 rabbits was clipped. Test material (500 mg premixed with water) was applied to the skin using a Hansamed - hypoallergenic wound plaster. Another plaster with just the vehicle and not the test substance was also applied beside the test substance. The applications were fastened so that the animal could not remove it or orally raise it.

The extent of erythema, crust formation, edema and all other remarkable findings were scored according to the method of Draize at 1, 24, 48 and 72 hours.

Reliability : (2) valid with restrictions
Guideline study. However, purity of the test material was not listed.

27.07.2004 (1)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure time	:	24 hour(s)
Comment	:	rinsed after (see exposure time)
Number of animals	:	3
Vehicle	:	water
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : There were no departures from the guidelines that would have influenced either the validity or the interpretation of the results of these studies.

The study was translated from German to English.

Result : Scoring was negative for turbidity, reddening, swelling erythema and crust formation or edema formation or cornea surface changes. All scores were zero. The test substance was not irritating or corrosive to eyes.

Test condition : Time period of the study: Jan. 31 to Feb. 7, 1989

Test substance: The stability of the test substance was guaranteed over the duration of the study. It was stored at room temperature in absence of light. It was a gold powder. The pH of a 100 g/l solution was 7.

Animals: All animals were healthy adult, female albino rabbits of the strain HC:NZW (breeder: Interfauna UK Ltd.). The animals weighed 3.4, 3.0, and 3.8 kg. They had never been mated. The rabbits were kept under standard conditions in single cages and allowed free access to standard rabbit chow and water. Animals were identified using ear tags and by their cages. The rabbits were quarantined for at least 14 days before the study. Shortly after arrival, they were examined collectively for Coccidien Oocysten. After the adaptation phase all animals were examined one day before the study to assure they were healthy. Only healthy symptom free animals were used. There was no vaccination or treatment with anti-infective agents. Room conditions were 20 +/-3 degrees C, 50% relative humidity, 12/12 hour light/dark cycle, and 10 air changes/hr.

Study conduct: The animals were weighed on the first day of the study immediately before exposure. Each rabbit was treated with 100 microliters of the test material. This was an application of about 90 mg of the test material. After the application the lids were rubbed back and forth about one second and held together. The other eye was not treated and served as control. The treated eye was rinsed out 24 hours later with a physiological NaCl solution.

At 1, 24, 48, 72 hours and 7 and 14 days, the condition of the cornea (degree of clouding and afflicted surface), iris (hyperemia, reaction to light), conjunctiva (erythema and chemosis) and the tear flow (outflow) were scored according to the Draize method. Also observed was the turbidity of the chamber water and any remarkable observations. One drop of a 1% fluorescein solution was applied on the surface of the cornea to detect defects in the epithelium of the cornea. Following examination, the eyes were rinsed with physiological NaCl solution. Uv light was used to help detect afflictions. Only results that persisted 24 hours or longer were scored. Photographs were taken of any findings of special relevance that persisted after 72 hours.

Reliability : (2) valid with restrictions
Guideline study. However, purity of the test material was not listed.

27.07.2004 (1)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Remark : No data available. Endpoint does not need to be filled for this material, which is only included in the category to provide supplemental information.

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	S. typhimurium strains TA98, TA100, TA1535 and TA1537
Test concentration	:	up to 5000 micrograms/plate
Cytotoxic concentr.	:	> 5000 micrograms/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: EEC Directive 84/449/EEC and OECD Test Guideline 471
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : The test material was stable in the vehicle at room temperature at concentrations ranging from 0.08 mg/l to 50 mg/l for at least four hours.

Result : There was no indication of a bacteriostatic effect of the test material at doses up to and including 5000 micrograms/plate. The test material was not mutagenic in the absence or presence of S-9 in either study. All of the positive controls induced at least the required increases in mutants for both experiments to be considered valid. In each experiment, all other criteria for a valid experiment were met.

Test condition : Bacteria: The original strains were obtained from Dr. Bruce Ames on December 12, 1986. Stock cultures were treated with DMSO to protect against the effects of freezing and then were stored at -80 degrees C in 1 ml portions. Cultures used in the test came from stocks that had satisfactory crystal violet and UV sensitivities. A special test for ampicillin resistance was not necessary since strains TA100 and TA98 were incubated on ampicillin-containing agar and formed individual colonies.

Controls: The solvent control was DMSO. The positive controls were 10 micrograms/plate sodium azide for strain TA1535 without S-9, 0.2 micrograms/plate nitrofurantoin for strain TA100 without S-9, 4-nitro-1,2-phenylene diamine for strains TA1537 (10 micrograms/plate) and TA98 (0.5 micrograms/plate) without S-9, and 3 micrograms/plate 2-aminoanthracene for all strains with S-9.

Test material: The material was dissolved in DMSO and tested at 8, 40, 200, 1000 and 5000 micrograms/plate. The highest dose used (5000 micrograms/plate) was specified by the protocol.

S-9 mix: S-9 was obtained from the livers of at least six adult, male Sprague-Dawley rats (200-300 g) that had been injected i.p. with 500 mg/kg Aroclor 1254 five days before euthanization. S-9 mix (30% S-9 and 70% cofactor solution) was prepared on the day of use and kept on ice during the experiment. Prior to first use, each batch was checked for metabolic activity against reference mutagens.

Study conduct: The bacterial suspensions were obtained from 17-hour cultures in nutrient broth (at 37 degrees C). No standardized procedure was employed to set the bacterial suspensions at a defined density, since the chosen method of incubation normally produced the desired density. Suspensions were diluted 1: 1,000,000 for determining the titer. Titers were determined under the same conditions as mutations, except that the histidine concentration in the soft agar was increased from 0.5 mM to 2.5 mM to permit the complete growth of bacteria.

The study was performed twice (April 26, 1991 and May 10, 1991). In each study, four plates (both with and without S-9 mix) were prepared per concentration of test material and negative and positive controls. The first test was considered a pre-test for toxicity. Doses in the second test were dependent on the results of the first. Test material, negative or positive control (0.1 ml) was mixed with 0.1 ml of bacteria, 0.5 ml of buffer (or S-9 mix, and 2.0 ml of soft agar. The mixture was then poured onto Petri dishes containing solid agar. The cells were incubated for 48 hours at 37 degrees C, and colonies were counted with an automatic colony counter.

Criteria for acceptability: The assay was considered acceptable if the frequencies of mutants in the negative controls were within expected range, the positive controls induced significant increases in mutants, and the density of bacteria used was sufficient. Even if the criteria for acceptability were not met, an assay was accepted if the test material tested positive.

Criteria for a positive result: The test material was considered to be mutagenic if there was a reproducible and dose-related increase in mutants in at least one strain. For all strains except TA1537 (where a 3-fold increase was considered positive), a doubling of the control frequency was

considered a positive response.

Test substance : The test material contained 64.4% CAS No. 78447-91-3, 24.6% H2O, 9.91% potassium, 1.42% sodium and 1.2% sulfate.

Reliability : (2) valid with restrictions
Study was comparable to a guideline study with acceptable restrictions. Four strains were used instead of five.

Flag : Critical study for SIDS endpoint
08.07.2004 (9)

Remark : No chromosome aberration data are available. This endpoint does not need to be filled for this material, which is only included in the category to provide supplemental information.

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Remark : No data available. Endpoint does not need to be filled for this material, which is only included in the category to provide supplemental information.

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Remark : No data available. Endpoint does not need to be filled for this material, which is only included in the category to provide supplemental information.

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

(1) Bayer AG (1989). Report No. 17819, dated 14.3.1989 (unpublished study).

(2) Bayer AG (1989). Study of the acute oral toxicity in male and female Wistar rat. Report No. 18306, dated 28.8.1989 (unpublished study).

(3) Bayer AG (1989). Final report: Water solubility, CAS No 78447-91-3. Study number A 88/0068/01. March 14, 1989 (unpublished study).

(4) Bayer AG, Unpublished study (no date available).

(5) Bayer AG (1991). Berechnung UWS-Produktsicherheit. [Translated as, “Calculation UWS Product Safety.”]

(6) Ciba Geigy (1989). Biological breakdown of Dinitrostilbendisulfonic acid. Test number 72A/89 (unpublished study).

(7) Ciba Geigy (1989). Oxygen Consumption Test with Industrial Sludge. Study Number 72A/89 (unpublished).

(8) Fraunhofer-Institut fuer Umweltchemie and Oekotoxikologie (1989). Fish, Acute Toxicity (Fische, Akute Toxizitaet) (unpublished study).

(9) Herbold BA (1992). Dinitrostilbenedisulfonic acid K Salmonella/Microsome test. Bayer AG Study No. T 8039628, dated 23.1.1992 (unpublished).

(10) Marchold JV (1972). Sbornik Vysledku Toxikologickeho Vysetreni Latek A Pripravku, Institut Pro Vychovu Vedoucicin Pracovniku Chemicke-ho Prumyclu, Praha, Czechoslovakia, 194.

(11) Zaitseva NV and Kulikov AL (1980). Gig Sanit (3): 73-76.

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

06 JAN -9 AM 10:43

201-16114

IUCLID

Data Set

Existing Chemical	:	ID: 7336-20-1
CAS No.	:	7336-20-1
EINECS Name	:	disodium 4,4'-diaminostilbene-2,2'-disulphonate
EC No.	:	230-847-3
TSCA Name	:	Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis[5-amino-, disodium salt
Molecular Formula	:	C14H14N2O6S2.2Na

Producer related part

Company	:	PCA Services, Inc
Creation date	:	24.05.2004

Substance related part

Company	:	PCA Services, Inc
Creation date	:	24.05.2004
Status	:	
Memo	:	
Printing date	:	16.12.2005
Revision date	:	16.12.2005
Date of last update	:	16.12.2005
Number of pages	:	51
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	
Name	:	3V Sigma S.p.A.
Contact person	:	
Date	:	
Street	:	Via A. Moro, 28

Town	:	24030 Mozzo Bergamo
Country	:	Italy
Phone	:	(35) 61 13 34
Telefax	:	(35) 46 15 12
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Type	:	
Name	:	Bayer AG
Contact person	:	
Date	:	
Street	:	
Town	:	51368 Leverkusen
Country	:	Germany
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	
Smiles Code	:	
Molecular formula	:	C14H14N2O6S2.2Na
Molecular weight	:	414.37
Petrol class	:	

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1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organometallic
Physical status	:	solid
Purity	:	
Colour	:	
Odour	:	

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

2,2'-Stilbenedisulfonic acid-4,4'-diamino, disodium salt

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4,4'-DIAMINO-2,2'-(1.2-ETHENDIYL)BIS(5-AMINOBENZOLSULFONSAEURE), DI-NATRIUM-SALZ

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

4,4'-DIAMINO-2,2'-STILBENEDISULFONSAEURE, DINATRIUMSALZ

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

4,4'-DIAMINOSTILBEN-2,2'-DISULFONSAEURE, DINATRIUMSALZ

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

4-4' Diamino-2,2'-stilbendisulfonic acid, flavonic acid disodium salt

Source : 3V Sigma S.p.A. Mozzo Bergamo
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

BENZENESULFONIC ACID, 2,2'-(1,2-ETHENEDIYL)BIS(5-AMINO-, DISODIUM SALT

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

FLAVONSAEURE S

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

P,P'-DIAMINODIPHENYLETHYLEN-O,O'-DISULFONSAEURE, DINATRIUMSALZ

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

P,P'-DIAMINOSTILBEN-O,O'-DISULFONSAEURE, DINATRIUMSALZ

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : industrial
Category :

09.02.2004

1.7.1 DETAILED USE PATTERN

Industry category : 13 Textile processing industry
Use category :
Extra details on use category : No extra details necessary
No extra details necessary
Emission scenario document : available
Product type/subgroup :
Tonnage for Application :
Year :
Fraction of tonnage for application :
Fraction of chemical in formulation :
Production : :
Formulation : :
Processing : :
Private use :
Recovery :

09.02.2004

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by	:	other: Bayer AG
Labelled by	:	other: Bayer AG
Class of danger	:	1 (weakly water polluting)
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-Feb-2000.

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation	:	
Substance listed	:	no
No. in Seveso directive	:	
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-Feb-2000.

1.8.5 AIR POLLUTION

Remark	:	no classification
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-Feb-2000.

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	> 300 °C
Sublimation	:	
Method	:	OECD Guide-line 102 "Melting Point/Melting Range"
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Test condition	:	Anthraquinone was used as a reference chemical to validate accuracy of the thermometer and melting point apparatus. The heating rate was 1 degree C per minute. A correction of 1 degree was applied to the thermometer. Before testing the sample was dried for 24 hours at room temperature over phosphorus pentoxide under a water stream vacuum.
Result	:	No sign of melting was observed up to 300 degrees
Reliability	:	(2) valid with restrictions. Guideline study without detailed documentation. Purity of test substance was not given.
Flag	:	Critical study for SIDS endpoint

16.12.2005 (7)

Value		349.84 °C
Decomposition		
Method		other: calculation using MPBPWIN (v1.41), inputting CAS No 7336-20-1
Year		2005
GLP		no
Test substance	:	as prescribed by 1.1 - 1.4.
Remark	:	Since the substance is a salt, it will have a melting point above 300 degrees C, as is consistent with other members of the category.
Reliability	:	(2) valid with restrictions Data were obtained by model estimation.

2.2 BOILING POINT

Remark	:	Since the substance is a salt, a boiling point is irrelevant for this material.

2.3 DENSITY

Type	:	bulk density
Value	:	ca. 650 kg/m3 at 20 °C
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Source	:	3V Sigma S.p.A. Mozzo Bergamo EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004

Type	:	bulk density

Value	:	650 kg/m3 at 20 °C
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (2)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Remark	:	No data available. Since the substance is a salt, and does not exist as a neutral molecule, it cannot exist in vapor form or exert a meaningful vapor pressure.

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	-3.99
pH value	:	
Method	:	other: calculated using EPIWINKOWWIN (v1.67), inputting CAS No. 7336-20-1.
Year	:	2005
GLP	:	
Test substance	:	as prescribed by 1.1 -1.4
Reliability	:	(2) valid with restrictions. Value was obtained by modeling.
Flag	:	Critical study for endpoint

Partition coefficient	:	
Log pow	:	-1.7 at °C
pH value	:	
Method	:	other (calculated): Leo, A.: CLOGP-3.54 MedChem Software 1989. Daylight, Chemical Information Systems, Claremont, CA 91711, USA
Year	:	
GLP	:	
Test substance	:	other TS: CAS No. 81-11-8 (free acid)
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (5)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	water
Value	:	> 100 g/l at 21 °C
pH value	:	
concentration	:	
Temperature effects	:	

Examine different pol.	:	
pKa	:	
Description	:	soluble (1000-10000 mg/L)
Stable	:	
Deg. product	:	
Method	:	other: internal company procedure
Year	:	
GLP	:	no data
Test substance	:	other TS: 72.6% purity (active ingredient CAS 7336-20-1), + 4.4 % Natrium Chloride
Reliability	:	(2) valid with restrictions Manufacturer data without detailed documentation.
Flag	:	Critical study for SIDS endpoint

16.12.2005 (8)

Solubility in	:	water
Value	:	= 100 g/l at 20 °C
pH value	:	ca. 7
concentration	:	.1 vol% at 20 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	soluble (1000-10000 mg/L)
Stable	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Source	:	3V Sigma S.p.A. Mozzo Bergamo EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (2)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Remark	:	n.a.
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	water
Light source	:	other: photoreactor
Light spectrum	:	= 254 nm
Relative intensity	:	
Conc. of substance	:	.00005 mol/l at °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	.017 mg/l
Rate constant	:	= .055 cm^3/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	other (measured)
Year	:	1996
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	The purpose of the study was to determine the degradative rate constant for various micropollutants, including the stilbene test material, in the presence of hydrogen peroxide and uv radiation. Also to determine the effect of added bicarbonate ion on this process. Photochemical oxidation using hydrogen peroxide is a promising method of eliminating hydrophilic xenobiotics, such as 4,4'diaminostilbene-2,2'-disulfonate from water.
Result	:	The measured first order rate constant was 0.055 1/S (reciprocal seconds) in the absence of added bicarbonate ion. The rate constant increased with increasing bicarbonate ion concentration.
Test condition	:	Standard commercial test product was dissolved in demineralized water at the stated concentration. Hydrogen peroxide was added at the stated concentration. The resultant mixed solution was irradiated using a photoreactor, and the photon flux was determined by uranyl oxalate actinometry. The pH of the solution was measured to be 6.1+/- 0.1. The concentrations of test material were measured at various times using ion-pair chromatography, using a Hewlett Packard 1090 liquid chromatograph with a HP 79883 B diode array detector and a HP 1046 A fluorescence detector. Degradation of the test material was recorded as a function of reaction time, and the data were fitted to a first-order rate model: ln(c/c(initial) = -k(deg) x t, where c and c(initial) are the concentrations at irradiation time t (in seconds) and at the beginning of the reaction (t = 0 sec), respectively. K(deg) is the first-order rate constant in 1/sec. Other runs were made determining the rate constant at various concentrations of added bicarbonate ion, in order to determine the effect due to scavaging of hydroxyl radical with bicarbonate. In the case of the stilbene test material, increasing bicarbonate concentrations increased the rate constant, because of increasing concentrations of bicarbonate radical, which is capable of oxidizing and degrading the stilbene.
Test substance	:	Commercially available material, without further purification. Purity not noted.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment. Non-standard study. Measured degradation rate constants of the oxidative degradation of test material with hydroxyl radical generated from added hydrogen peroxide by uv radiation. Temperature not noted but assumed to be room temperature. Purity of test substance not noted.

(15)

Remark	:	This material does not volatilize to any degree, since it is an ionized, organic salt. Therefore, it will not be found in any significant concentration in the atmosphere other than in particle form. For this reason, atmospheric photodegradation is not an appreciable or important degradative pathway.
Reliability	:	(2) valid with restrictions. Information is based on chemical structure.

3.1.2 STABILITY IN WATER

Remark	:	No data available. The substance does not contain any functional groups subject to hydrolysis, and should be stable in water.

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other: air, water, soil, biota
Air	:	1.32 E-23 % (Fugacity Model Level III)
Water	:	57.93 % (Fugacity Model Level III)
Soil	:	% (Fugacity Model Level I)
Biota	:	.107 % (Fugacity Model Level II/III)
Soil	:	42 % (Fugacity Model Level II/III)
Method	:	other: calculation using EPIWIN v3.11
Year	:	2005
Result	:	Half-lives in various media are air:1.181 hours; water: 900 hours; soil: 900 hours; and sediment: 3600 hours. The Henry's Law Constant [calculated by EPIWIN HENRY (v3.10)] is 3.4 E-23 atm-m3/mol (bond est.). The soil-sediment coefficient [calculated by EPIWIN PCKOC (v1.66)] is Koc = 4.85.E+3.
Test condition	:	Inputs to the model are CAS No. 7336-20-1 and emission rates: air: 0 kg/hr, water: 1000 kg/hr, and soil: 1000 kg/hr.
Reliability	:	(2) valid with restrictions Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge
Contact time	:	56 day(s)

Degradation	:	< 15 (±) % after 56 day(s)
Result	:	not readily biodegradable
Deg. product	:	
Method	:	OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year	:	1992
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Result	:	The only result given was that the material degraded < 15% over 56 days. The curve was not included in the report.
Test condition	:	Activated sludge (concentration not listed), mineral nutrients and the test material (concentration not listed) in an aqueous solution were placed together in a 1 – 4 liter glass vessel equipped with an agitator and an aerator. The test material was the only carbon source. The mixture was agitated and aerated at 22 degrees C (+/- 3 degrees) under diffuse illumination or in a dark room for up to 28 days. Degradation was monitored by determination of the DOC (or COD) values in the filtered solution at regular time intervals (not stated). The ratio of eliminated DOC (or COD) after each interval to the value at the start was expressed as percentage biodegradation. The results were plotted against time to give a biodegradation curve.
Test substance	:	Purity of the test material was not listed.
Reliability	:	(2) valid with restrictions Basic data given.
Flag	:	Critical study for SIDS endpoint

19.07.2004 (9)

Type	:	aerobic
Inoculum	:	predominantly domestic sewage, adapted
Contact time	:	
Degradation	:	0 (±) % after 20 day(s)
Result	:	under test conditions no biodegradation observed
Deg. product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	1977
GLP	:	no
Test substance	:	other TS: ca. 65 % active ingredient
Remark	:	related to BOD
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (2)

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	100 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	
Degradation	:	0 (±) % after 28 day(s)
Result	:	under test conditions no biodegradation observed
Deg. product	:	
Method	:	OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year	:	1986
GLP	:	no
Test substance	:	other TS: 72.6 % active ingredient

Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (2)

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	19 mg/l related to TOC related to
Contact time	:	
Degradation	:	0 (±) % after 21 day(s)
Result	:	under test conditions no biodegradation observed
Deg. product	:	
Method	:	other: modified OECD Confirmatory test
Year	:	1986
GLP	:	no
Test substance	:	other TS: 72.6 % a.i.
Remark	:	The TOC content of the test substance was 31.4% by the test and 33.1% by elemental analysis.
Reliability	:	(2) valid with restrictions Guideline study without detailed documentation.

16.12.2005 (7)

Contact time	:	
Degradation	:	ca. 5 (±) % after 28 day(s)
Result	:	other
Deg. product	:	
Method	:	OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year	:	
GLP	:	no data
Test substance	:	
Remark	:	Considering the strict test conditions, a low biodegradation value does not necessarily imply that the product may not undergo biological degradation when environmental conditions apply.
Source	:	3V Sigma S.p.A. Mozzo Bergamo EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000. No reference was listed in this document.

08.07.2004

3.6 BOD5, COD OR BOD5/COD RATIO

BOD5

Method	:	ISO 5815 "Water quality - Determination of biochemical oxygen demand after 5 days (BOD5) - Dilution and seeding method"
Year	:	
Concentration	:	related to
BOD5	:	mg/l
GLP	:	
Source	:	3V Sigma S.p.A. Mozzo Bergamo

EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000. No reference was listed in this document.

08.07.2004

Remark : COD : 972 mg/g
TOC : 342
Test substance: 72.6 % a.i.

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (2)

Remark : BOD5 by Method A-15 is 0 mg/g 02. BOD/COD = .00
COD by Method A-22 is 1000mg/g O2. BOD/TOC = 1.13
pH: 6.9
concentration: 1g/l
Test substance: 72.6 % a.i.

Reliability : (2) valid with restrictions
Guideline study without detailed documentation

16.12.2005 (7)

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	> 500
Limit test	:	
Analytical monitoring	:	no
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1986
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Results	:	None of the fish exposed to 1, 10, 100 or 500 mg/l (in either test) died or exhibited unusual behavior.
Test condition	:	Species: Brachydanio rerio. Length and weight were not listed. Water conditions: Pretest: The temperature of the water containing 1, 10 and 100 mg/l decreased from 25.6 to 20.2 over the course of the experiment. The temperature of the water containing 500 mg/l increased from 20.6 to 22.6 degrees over time. For all test conditions, the O2 saturation of test water ranged from 8.9 – 9.1 mg/l at the beginning of the test and 8.4 – 8.8 mg/l at the end of the test. The pH of the water ranged from 6.5 – 6.8 for all test conditions. No other water conditions were listed. Final test: The temperature, oxygen saturation and pH of the water ranged from 21.2 – 25.7 degrees, 8.0 – 8.9 mg/l and 6.4 – 7.2 throughout the test. Since the initial pH was 7.2 and pH of the water at 24 and 96 hours was 6.4 and 6.8 (respectively), it appears that addition of 500 mg/l test material to the water initially lowered the pH, but the water was sufficiently buffered to prevent any further decreases in pH. No other water conditions were listed. Test material: A stock solution of 1 g/l was prepared and stirred overnight. Aliquots of this solution were added to test flasks to obtain required concentrations. Conduct of study: A pretest was carried out using concentrations of 1, 10, 100 and 500 mg/l, and a final test was conducted using 500 mg/l. Ten fish were tested per concentration. The numbers of fish exhibiting unusual behavior or death were counted at 24, 48, 72 and 96 hours.
Test substance	:	Purity of the test material was not listed.
Reliability	:	(2) valid with restrictions Guideline study without detailed documentation.
Flag	:	Critical study for SIDS endpoint

08.07.2004 (3)(9)

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	>= 1000
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Method A-11
Year	:	1986

GLP	:	no
Test substance	:	other TS: 72.6 % a.i.
Reliability	:	(2) valid with restrictions. Meets generally accepted scientific standards. Study details were not provided.

08.07.2004 (7)

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	72 hour(s)
Unit	:	mg/l
LC0	:	>= 1000
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Bestimmung der akuten Wirkung von Stoffen auf Fische. Arbeitskreis "Fischtest" im Hauptausschuss "Detergentien" (15.10.73)(Translated as, “Determination of the acute effect of substance on fish in important application. “Detergents.”).
Year	:	1975
GLP	:	no
Test substance	:	other TS: ca. 65 % a.i.
Remark	:	Only 2 fish were tested. Results were written in a table.
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Documentation insufficient for assessment.

08.07.2004 (2)

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC0	:	= 200
Source	:	3V Sigma S.p.A. Mozzo Bergamo EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000. The reference was not listed in this document.

08.07.2004

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna Strauss
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	300…500
Analytical monitoring	:	no
Method	:	OECD Guide-line 202
Year	:	1986
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	A control for this test was not documented, but historical control data were maintained in a separate file that was not available. Water condition data were not presented. The EC50 value was not calculated by study

personnel.

Result : First test: Low levels of immobilization were noted at all concentrations from 1 to 90 mg/l (1or 2 out of 20), so a second test was initiated.

Second test: The results are presented below.

	Results (number immobilized)				
Dose (mg/l)	Replicate 1	Replicate 2	Replicate 3	Replicate 4	Total
50	0/5	0/5	0/5	0/5	0/20
70	0/5	0/5	0/5	0/5	0/20
100	0/5	0/5	0/5	0/5	0/20
200	1/5	0/5	0/5	2/5	3/20
300	0/5	2/5	0/5	0/5	2/20
500	3/5	2/5	2/5	4/5	11/20

The EC0 and EC100 values in the second test were 100 and > 500 mg/l, respectively. From the data presented, it appears that the EC50 value is > 300 and < 500 mg/l.

Test condition : Two separate tests were conducted. In the first test, twenty daphnids (4 replicates, 5 organisms per replicate) were exposed to 0.1 or 0.5 (indecipherable), 1, 5, 10, 50, 70 and 90 mg/l. In the second test, twenty daphnids (4 replicates, 5 organisms per replicate) were exposed to 50, 70 100, 200, 300 and 500 mg/l. In both tests, Daphnia were exposed for 48 hours and swimming ability was assessed.

Test substance : Purity of the test material was not mentioned.

Reliability : (2) valid with restrictions
Guideline study without detailed documentation.

Flag : Critical study for SIDS endpoint

07.07.2004 (4)(7)

Type :
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
EC0 : 100
EC100 : > 500
Analytical monitoring : no
Method : Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year : 1986
GLP : No
Test substance : other TS: 72.6 % a.i.

Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (2)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species :
Endpoint : biomass
Exposure period : 72 hour(s)
Unit : mg/l
EC50 : > 100

Limit test	:	
Analytical monitoring	:	no data
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	1992
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Result	:	The only result listed was the LC50 value (> 100 mg/l).
Test condition	:	Exponentially-growing cultures of selected green algae (Scenedesmus subspicatus, Selenastrum capricornutum or Ankistodesmus bibraianus) were exposed to various concentrations of test material over several generations under defined conditions. The exact species used was not listed. Growth inhibition in relation to controls was determined over 72 hours. No other information about test conditions was listed.
Test substance	:	Purity of the test material was not listed.
Reliability	:	(2) valid with restrictions Guideline study without detailed documentation.
Flag	:	Critical study for SIDS endpoint

07.07.2004 (9)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	activated sludge
Exposure period	:	3 hour(s)
Unit	:	mg/l
EC50	:	> 100
Analytical monitoring	:	no
Method	:	other: internal company procedure
Year	:	1986
GLP	:	no
Test substance	:	other TS: 72.6 % active ingredient
Reliability	:	(2) valid with restrictions Manufacturer data without detailed documentation.

16.12.2005 (7)

Type	:	aquatic
Species	:	activated sludge
Exposure period	:	
Unit	:	mg/l
BST	:	> 300
Analytical monitoring	:	no
Method	:	other: Bestimmung der Schadwirkung gegen Abwasserbakterien nach dem Truebungstest (ETAD, 1976) [Translated as, “Determination of the harmful effect with respect to waste water bacteria according to the turbidity test (ETAD, 1976)].
Year	:	1986
GLP	:	no
Test substance	:	other TS: 72.6 % active ingredient
Remark	:	exposure time: 16-20 h
Reliability	:	(2) valid with restrictions Manufacturer data without detailed documentation.

16.12.2005 (7)

Type	:	aquatic
Species	:	Photobacterium phosphoreum (Bacteria)
Exposure period	:	45 minute(s)
Unit	:	mg/l

EC50	:	> 500
Analytical monitoring	:	no
Method	:	
Year	:	1987
GLP	:	no
Test substance	:	other TS: 72.6 % active ingredient
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (1)

Type	:	aquatic
Species	:	Pseudomonas fluorescens (Bacteria)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	1000
Analytical monitoring	:	no
Method	:	other: Bestimmung der biologischen Schadwirkung toxischer Abwaesser gegen Bakterien. DEV, L 8 (1968) modifiziert (Translated as, “Determination of the biological harmful effect of toxic wastewater toward bacteria. DEV, L 8 (1968) Modified).”
Year	:	1975
GLP	:	no
Test substance	:	other TS: ca. 65 % active ingredient
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (2)

Type	:	other
Species	:	Pseudomonas fluorescens (Bacteria)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	= 1000
Source	:	3V Sigma S.p.A. Mozzo Bergamo EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000. The reference was not listed in this document.

08.07.2004

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

Type	:	animal
Deg. product	:	
Result	:	97% eliminated via urinary excretion (i.v. infusion) Radiolabel recovery in faeces after oral administration: 80 to 92%.
Source	:	3V Sigma S.p.A. Mozzo Bergamo EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000. The reference was not listed in this document.

08.07.2004

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	
Vehicle	:	
Doses	:	
Test substance	:	as prescribed by 1.1 – 1.4
Result	:	None of the animals died or exhibited signs of toxicity.
Test condition	:	Ten male rats (160 – 180 g) were treated by gavage with 5 g/kg test material in water. They were housed 5 per cage and observed for 14 days.
Reliability	:	(2) valid with restrictions Basic data given.
Flag	:	Critical study for SIDS endpoint

08.07.2004 (12)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	500 mg
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	3
Vehicle	:	water
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Only three animals were tested in accordance with the German Animal Protection Act.
Result	:	All scores were 0, with the exception of one score of one (barely perceptible erythema) at 24 hours. The average irritation indices were 0, 0.3 and 0 in the three animals.
Test condition	:	Animals: Three healthy, adult, male rabbits (strain HC:NZW) weighing 3.7,

3.5 and 3.0 kg were used in the study. They were quarantined for at least 14 days before use. During this period, pooled feces specimens were examined for Coccidia oocysts. Rabbits were individually housed in stainless steel cages under standardized conventional conditions (21 +/- 1.5 degrees C, 40-70% relative humidity, 12 hour light/dark cycle, 500 lux illumination, 12-15 air exchanges per hour). They were fed 100-120 g standard diet per animal/day and allowed free access to tap water. The animals were examined one day prior to use. Only animals not exhibiting any alterations to skin or eyes were used.

Test conduct: Approximately 24 hours before the test, fur was clipped from the dorso-lateral area of the trunk (6 x 6 cm) of each of the rabbits. Care was taken to avoid abrasion. Pulverized test material (500 mg) was moistened with deionized water and applied to a hypoallergenic patch. An additional patch as moistened only with water. The patches were placed on the opposite dorso-lateral areas of the trunk of each animal. They were held in place with a semiocclusive dressing for 4 hours. The area of exposure was approximately 6 cm2. After 4 hours, dressings were removed and the exposed skin was carefully washed with water.

Dermal irritation was scored for the degree of erythema/eschar formation according to the method of Draize after 1, 24, 48, and 72 hours and 7 days. Erythema/eschar and edema were each scored on a scale of 0-4 (no effect to severe effect). Any serious lesions or toxic effects other than dermal irritation were recorded. The Draize scores at 24, 48 and 72 hours were added. The total of the three scores was divided by three to give the irritation index. This index was calculated separately for erythema/eschar formation and edema. Data interpretation was based on the individual indices of the two most sensitive animals.

All study-related documentation was archived, in compliance with GLP.

Reliability : (2) valid with restrictions
Guideline study. However, test material purity was not listed.

21.07.2004 (11)

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
PDII :
Result : not irritating
Classification : not irritating
Method :
Year :
GLP :
Test substance :

Source : 3V Sigma S.p.A. Mozzo Bergamo
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

21.07.2004 (13)

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :

Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	
Method	:	other: see remarks
Year	:	
GLP	:	
Test substance	:	
Remark	:	Exposure time: 24 h, ear, 500 mg/animal, semi-occlusive, observation time: 7 d.
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

21.07.2004 (17)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1993
GLP	:	yes
Test substance	:	other TS: free acid (CAS 81-11-8)
Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (6)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	39 other: mg
Exposure time	:	24 hour(s)
Comment	:	
Number of animals	:	3
Vehicle	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Only three animals were tested in accordance with the German Animal Protection Act.
Result	:	A conjunctival redness score of 2 (diffuse, crimson color, individual vessels

not easily discernable) was observed in 1 rabbit at 1 hour and a conjunctival redness score of 1 (some blood vessels definitely hyperemic) was observed at 1 hour in the other 2 rabbits. Two rabbits also had conjunctival redness scores of 1 at 24 hours. Swelling scores of 1 (swelling slightly above normal, including nictitating membrane) were observed in all rabbits at 1 hour and 1 rabbit at 24 hours. All other scores were 0.

The irritation indices in the 3 rabbits were 0.3 (conjunctival redness), 0 and 0.3 (for both conjunctival redness and swelling in one animal). Scores < 1 were considered to be indicative of no irritation.

Test condition : Animals: One healthy, adult, nulliparous, nonpregnant, female rabbit (strain HC:NZW) weighing 3.4 kg and two males weighing 3.3 and 3.4 kg were used in the study. They were quarantined for at least 14 days before use. During this period, pooled feces specimens were examined for Coccidia oocysts. Rabbits were individually housed in stainless steel cages under standardized conventional conditions (21 +/- 1.5 degrees C, 40-70% relative humidity, 12 hour light/dark cycle, 500 lux illumination, 12-15 air exchanges per hour). They were fed 100-120 g standard diet per animal/day and allowed free access to tap water. The animals were examined one day prior to use. Only animals not exhibiting any alterations to skin or eyes were used.

Test conduct: The lower lid was gently pulled away from the eyeball and a volume of 100 microliters of pulverized test material (approximately 39 mg) was placed into the conjunctival sac of one eye of each of the rabbits. The lids were then gently held together for about 1 second. The other eye remained untreated and served as the control. The treated eye was rinsed with normal saline 24 hours after treatment.

Eye irritation was scored and recorded at 1, 24, 48, and 72 hours and 7 days. The signs of cornea (opacity and area affected), iris (hyperemia, reaction to light), conjunctivae (erythema, chemosis), and discharge were recorded as described by Draize. The aqueous humor was scored for opacity as described by McDonald and Shadduck (in: Marzulli FN and Maibach HI (Eds.): Dermatotoxicology and Pharmacology (3rd. Ed.), Wiley, New York). Any serious lesions or toxic effects other than ocular were recorded. Examinations of the cornea, iris and aqueous humor were facilitated using optical instruments (e.g. hand slit lamp).

To define epithelial damage, one drop of a 1% fluorescein solution was applied to the corneal surface 24 hours after treatment. The eye was then rinsed with normal saline. The eyes were examined under UV light in an darkened room and under diffuse white illumination according to the method of McDonald and Shadduck. This procedure was repeated later if positive effects were noted.

Only effects persisting for more than 24 hours were included in the evaluation. The irritation indices/mean irritation indices were calculated for cornea (opacity), iris, and erythema and swelling (chemosis) of the conjunctivae. The interpretation was based on the individual indices obtained from the two most sensitive animals.

All study-related documentation was archived, in compliance with GLP.

Reliability : (2) valid with restrictions
Guideline study. However, test material purity was not listed.

21.07.2004 (11)

Species : rabbit
Concentration :
Dose :
Exposure time :

Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	moderately irritating
Classification	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	

Source	:	3V Sigma S.p.A. Mozzo Bergamo EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

21.07.2004 (13)

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	slightly irritating
Classification	:	
Method	:	other: 50 mg/animal, observation time: 7d
Year	:	
GLP	:	
Test substance	:	

Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

21.07.2004 (17)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	chronic
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	103 weeks
Frequency of treatm.	:	continuous
Post exposure period	:	none
Doses	:	0, 12500, 25000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	12500 ppm
LOAEL		25000 ppm
Method	:	other: NTP
Year	:	1992

GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : The information in this summary is consistent with the OECD dossier for CAS No. 81-11-8 presented at SIAM 4. The summary has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summary is presented within quotation marks. Methodological information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier for CAS No. 81-11-8 presented at SIAM 4.

The average amount of test material ingested by males from weeks 1-13 in was 765 mg/kg/day for 12500 ppm and 1529 mg/kg/day for 25000 ppm. During weeks 14-104, the average amount of test material ingested by males was 454.5 mg/kg/day for 12500 ppm and 962.5 mg/kg/day for 25000 ppm.

The average amount of test material ingested by females from weeks 1-13 was 841 mg/kg/day for 12500 ppm and 1715 mg/kg/day for 25000 ppm. During weeks 14-104, the average amount of test material ingested by females was 528 mg/kg/day for 12500 ppm and 1085.5 mg/kg/day for 25000 ppm.

The summary in the OECD IUCLID document stated that doses of 12500 and 25000 ppm in the rats were equivalent to 558 and 1151 mg/kg day, respectively. It also stated that "although the animals might have been able to tolerate slightly higher doses, results of the 13 week studies indicate that a doubling of the highest doses could not have been tolerated."

Result : 15 month examination: "There were no biologically significant absolute or relative organ weight, clinical pathology, or histopathology findings in rats administered disodium 4,4'-diamino-2,2'-stilbene disulfonate in feed for 15 months. "

Body weight, food consumption, survival and clinical findings: "Mean body weights were marginally decreased for high dose male and female rats. Food consumption by dosed rats was similar to food consumption by controls throughout the studies. Survival was similar among control and treated groups of rats. No clinical findings related to chemical administration were observed in rats."

Non-neoplastic and Neoplastic Effects: "There were no chemical-related increased incidences of neoplasms at any site. Ulcers of the forestomach or glandular stomach occurred in dosed rats (males: 1/10, 5/50, 4/50, females: 0/50, 1/50, 4/50). "

Test condition : Animals: Male and female F344/N rats were observed for 16 days before use. They were approximately 6 weeks old at the beginning of the studies. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 74 degrees F and 50 +/- 15.2 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Cages were rotated weekly. Five animals per sex were randomly selected and euthanized for parasite evaluation (negative) and gross observation of disease (negative). Groups of 60 rats/sex received feed containing 0, 12500, or 25000 ppm test material for 103 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The

homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed at least once every eight weeks to confirm stability.

Study conduct: Animals were observed twice daily and clinical observations were recorded weekly for 13 weeks, then monthly (or as necessary). Animals were weighed at the beginning of the study, weekly for 13 weeks, monthly through week 90, and every 2 weeks thereafter. Food consumption was measured once per month.

After 15 months, 10 animals per sex from each group were euthanized for interim examinations. Blood was withdrawn from the orbital sinus plexus of all surviving animals for hematological (hemoglobin, hematocrit, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total and differential leukocyte counts) and clinical pathology analyses (blood urea nitrogen, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase). The brain, liver and right kidney of each animal were weighed.

Necropsies were performed on all animals. All organs and tissues were examined for gross lesions and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all 15-month interim animals, all tissues with grossly visible lesions, all animals that died or were killed moribund prior to 21 months, and all control and high dose animals that survived to study termination. Tissues examined included the adrenal gland, bone (costochondrial junction), bone marrow (femur), brain, clitoral gland, esophagus, heart, kidney, large intestine, liver, lung, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, preputial gland, prostate, salivary gland, seminal vesicle, skin, small intestine, spleen, stomach, testis (with epididymis), thymus, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined from low dose animals that died or were killed moribund after 21 months or at study termination were gross lesions, adrenal gland, liver (males), kidney (females), mammary gland (females), pituitary gland (males) and spleen (males).

Statistical analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier. The possibility of a dose-related effect on survival was assessed using the methods of Cox and Tarone. Tumor incidence data were analyzed using a logistic regression analysis which assumed that the tumors were discovered as the result of death from an unrelated cause. The Fisher exact test and the Cochran-Armitage trend test were used to analyze the overall proportion of tumor-bearing animals. Organ and body weight data were analyzed using the multiple comparison procedures of Williams and Dunnett. Clinical chemistry and hematology data were analyzed using the multiple comparison methods of Shirley and Dunn. Jonckheere's test was used to assess the

significance of dose-response trends.

Quality check: All slides, blocks and residual tissues were sent to the NTP Archives for inventory, slide/block match and wet-tissue audit. All neoplastic diagnoses from a randomly selected 10% of the control and high dose rats were reevaluated by a different quality assessment pathologist. The NTP Pathology Working Group chair blindly reviewed selected tissues for which there was a disagreement between the laboratory and quality assessment pathologists.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in 27/28 dose formulations were within the acceptable range of +/- 10% of target concentrations at both analyses. The sample that was not within this range was remixed.

Conclusion : There was no evidence of carcinogenic activity in rats receiving 12500 or 50000 ppm test material. However, both doses were associated with slight increases in the incidences of ulceration of the forestomach or glandular stomach of both males and females. Judging from the NOEL assigned to the study, apparently this was not considered to be related to test material administration.

Reliability : (1) valid without restriction
Comparable to a guideline study

Flag : Critical study for SIDS endpoint

(16)

Type : sub-chronic
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 13 weeks
Frequency of treatm. : continuous
Post exposure period : none
Doses : 0, 6250, 12500, 25000, 50000 or 100000 ppm
Control group : yes, concurrent no treatment
NOAEL : 25000 ppm
LOAEL 50000 ppm
Method : other: NTP
Year : 1992
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : The information in this summary is consistent with the OECD dossier for CAS No. 81-11-8 presented at SIAM 4. The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

According to the OECD summary, a dose of 25000 ppm corresponds to 1207 mg/kg/day in rats.

Result : Mortality: "One female rat receiving 100000 ppm group died during the study."

Body weight: "Mean body weight gain was significantly decreased in male rats receiving 50000 or 100000 ppm and female rats receiving 100000

ppm."

Clinical findings: "Clinical findings in male [word "male" omitted in OECD summary] rats receiving 50000 or 100000 ppm or females receiving 100000 ppm were diarrhea, emaciation and hyperemia of the perineum."

Feed consumption: [these data were not present in the OECD summary] Feed consumption of males in the 100000 ppm group was 35% lower than that of controls during the first week, and remained lower than controls through week 8. Feed consumption of females in the 100000 ppm group was 27% lower than that of controls during the first week. By week 4, feed consumption of females in this group exceeded that of controls.

Organ weights and clinical chemistries: "There were no biologically significant changes in absolute or relative organ weights or clinical pathology results in rats."

Pathological examination: "Histopathologic lesions present in rats receiving 100000 ppm were bone marrow cellularity and chronic inflammation of the anus and rectum."

Test condition **:** Animals: Male and female F344/N rats were observed for 13-15 days before use. They were 6-7 weeks old at the beginning of the studies. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 70.4 degrees F and 43 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Groups of 10 rats/sex received feed containing 0, 6250, 12500, 25000, 50000 or 100000 ppm test material for 13 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed twice during the 13 week study to confirm stability.

Study conduct: Animals were observed twice daily and clinical observations were recorded weekly. Animals were weighed at the beginning of the study and weekly thereafter. Food consumption was measured weekly.

At the end of 13 weeks, rats were anesthetized and blood was withdrawn from the orbital sinus plexus of all surviving animals for clinical pathology analyses (glucose, total protein, albumin, albumin/globulin ratio, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase). Hematological analyses were not performed.

Necropsies were performed on all study animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. All animals that

died or were killed prior to the end of the study, all controls, and all high dose animals received complete histopathologic examinations. The aforementioned tissues plus the adrenal gland, bone and marrow (sternum), cecum, clitoral gland, colon, duodenum, esophagus, ileum, jejunum, left kidney, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, preputial gland, prostate, rectum, salivary gland, spleen, stomach, left testis, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Liver sections from the 0, 25000 and 100000 ppm groups were stained with Oil Red O and periodic acid-Schiff (with and without diastase). The rectum/anus from all groups was examined microscopically.

Statistical analyses: Body weight and absolute and relative (to body weight) organ weight data were analyzed using the Williams' or Dunnett's test. Clinical chemistry data were analyzed using Dunn's or Shirley's test. Incidences of pathological lesions were analyzed using the Fisher exact test. Feed consumption data were not analyzed statistically. The critical level of significance was p <= 0.05.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in the test diets were within the acceptable range of +/- 10% of target concentrations at both analyses.

Reliability : (2) valid with restrictions
Comparable to a guideline study with acceptable restrictions. Hematological analyses were not performed.

Flag : Critical study for SIDS endpoint

(16)

Type	:	sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	14 days
Frequency of treatm.	:	continuous
Post exposure period	:	
Doses	:	0, 6250, 12500, 25000, 50000 and 100000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	= 25000 ppm
LOAEL	:	= 50000 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 – 1.4

Remark : The information in this summary is consistent with the OECD dossier for CAS No. 81-11-8 presented at SIAM 4. The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

According to the OECD summary, a dose of 25000 ppm corresponds to 2315 mg/kg/day in rats.

Result : "All rats survived to the end of the study. The mean body weight gains of males receiving 50000 or 100000 ppm and of females receiving 100000

ppm were significantly lower than those of the respective controls. Clinical findings included diarrhea in the rats receiving 100000 ppm. There were no chemical-related changes in absolute or relative organ weights. There were no gross or microscopic lesions related to chemical administration."

Test condition : Animals: Male and female F344/N rats were observed for 15 days prior to exposure. Animals were 6-7 weeks old at study initiation. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 75 degrees F and 55.7 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Groups of 5 rats/sex received feed containing 0, 6250, 12500, 25000, 50000 or 100000 ppm test material for 14 days, followed by a 1 day observation period.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 5 minutes with and 10 minutes without an intensifier bar. Dose formulations were prepared weekly. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed once during the study to confirm stability.

Study conduct: Clinical observations were conducted twice daily. Animals were weighed at the start of the study, and on Days 8 and 16. Food consumption was recorded weekly. Complete necropsies were performed on all animals. The brain, heart, right kidney, liver, lungs and thymus of survivors were weighed at necropsy. All animals in the control and high dose groups received complete histopathologic examinations. Tissues examined included adrenal gland, bone and marrow (sternum), brain, clitoral or preputial gland, colon, esophagus, heart, jejunum, kidney, liver, lung, mammary gland, mandibular lymph node, nasal cavity, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder and uterus.

Statistical analyses: Data were examined using the Williams' or Dunnett's test. The critical level of significance was $p <= 0.05$.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Test material formulations were within 10% of target concentrations.

Reliability : (2) valid with restrictions
Duration of study was less than 28 days

08.07.2004 (16)

Type : chronic
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed

Exposure period	:	2 years
Frequency of treatm.	:	daily (feeding study)
Post exposure period	:	no
Doses	:	0, 6250 or 12500 ppm
Control group	:	yes
NOAEL	:	6250 ppm
LOAEL		12500 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : The information in this summary is consistent with the OECD dossier for CAS No. 81-11-8 presented at SIAM 4. The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Methodological information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

The average amount of test material ingested by males from weeks 1-13 was 836 mg/kg/day for 6250 ppm and 1738 mg/kg/day for 12500 ppm. During weeks 14-104, the average amount of test material ingested by males was 763 mg/kg/day for 6250 ppm and 1565 mg/kg/day for 12500 ppm.

The average amount of test material ingested by females from weeks 1-13 was 997 mg/kg/day for 6250 ppm and 2081 mg/kg/day for 12500 ppm. During weeks 14-104, the average amount of test material ingested by females was 666 mg/kg/day for 6250 ppm and 1444 mg/kg/day for 12500 ppm.

The summary in the OECD IUCLID document stated that doses of 6250 and 12500 ppm in the mice were equivalent to 776 and 1656 mg/kg day, respectively. It also stated that “although the animals might have been able to tolerate slightly higher doses, results of the 13 week studies indicate that a doubling of the highest doses could not have been tolerated.”

Result : 15 month examination: “There were no biologically significant absolute or relative organ weight, clinical pathology, or histopathology findings in mice administered disodium 4,4’-diamino-2,2’-stilbene disulfonate in feed for 15 months. “

Body weight, food consumption, survival and clinical findings: “Mean body weights were marginally decreased for high dose female mice. Food consumption by dosed mice was similar to food consumption by the controls throughout the studies. Survival was similar among control and treated groups of mice. No clinical findings related to chemical administration were observed in mice.”

Non-neoplastic and Neoplastic Effects: “There were no chemical-related increased incidences of neoplasm, non-neoplastic lesions, or other toxic effects in mice.”

Test condition : Animals: Male and female B6C3F1 mice were observed for 13 days before use. They were approximately 6 weeks old at the beginning of the studies. Animals were housed 5 per cage initially and allowed free access to food and water. Male mice were housed individually from weeks 39 to termination. Animals were housed under 74 degrees F and 50 +/- 15.2 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Cages were rotated weekly. Five animals per sex were randomly

selected and euthanized for parasite evaluation (negative) and gross observation of disease (negative). Groups of 60 mice/sex received feed containing 0, 6250, or 12500 ppm test material for 103 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed at least once every eight weeks to confirm stability.

Study conduct: Animals were observed twice daily and clinical observations were recorded weekly for 13 weeks, then monthly (or as necessary). Animals were weighed at the beginning of the study, weekly for 13 weeks, monthly through week 90, and every 2 weeks thereafter. Food consumption was measured once per month.

After 15 months, 10 animals per sex from each group were euthanized for interim examinations. Blood was withdrawn from the orbital sinus plexus of all surviving animals for hematological (hemoglobin, hematocrit, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total and differential leukocyte counts) and clinical pathology analyses (blood urea nitrogen, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase). The brain, liver and right kidney of each animal were weighed.

Necropsies were performed on all animals. All organs and tissues were examined for gross lesions and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all 15-month interim animals, all tissues with grossly visible lesions, all animals that died or were killed moribund prior to 21 months, and all control and high dose animals that survived to study termination. Tissues examined included the adrenal gland, bone (costochondrial junction), bone marrow (femur), brain, esophagus, gallbladder, heart, kidney, large intestine, liver, lung, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, prostate, salivary gland, seminal vesicle, skin, small intestine, spleen, stomach, testis (with epididymis), thymus, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined from low dose animals that died or were killed moribund after 21 months or at study termination were gross lesions, liver (males) and lung.

Statistical analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier. The possibility of a dose-related effect on survival was assessed using the methods of Cox and Tarone. Tumor incidence data were analyzed using a logistic regression

analysis which assumed that the tumors were discovered as the result of death from an unrelated cause. The Fisher exact test and the Cochran-Armitage trend test were used to analyze the overall proportion of tumor-bearing animals. Organ and body weight data were analyzed using the multiple comparison procedures of Williams and Dunnett. Clinical chemistry and hematology data were analyzed using the multiple comparison methods of Shirley and Dunn. Jonckheere's test was used to assess the significance of dose-response trends.

Quality check: All slides, blocks and residual tissues were sent to the NTP Archives for inventory, slide/block match and wet-tissue audit. All neoplastic diagnoses from a randomly selected 10% of the control and high dose rats were reevaluated by a different quality assessment pathologist. The NTP Pathology Working Group chair blindly reviewed selected tissues for which there was a disagreement between the laboratory and quality assessment pathologists.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in 27/28 dose formulations were within the acceptable range of +/- 10% of target concentrations at both analyses. The sample that was not within this range was remixed.

Reliability : (1) valid without restriction
Comparable to a guideline study

Flag : Critical study for SIDS endpoint

(16)

Type : sub-chronic
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 13 weeks
Frequency of treatm. : continuous
Post exposure period : none
Doses : 0, 6250, 12500, 25000, 50000 or 100000 ppm
Control group : yes, concurrent no treatment
NOAEL : 12500 ppm
LOAEL 25000 ppm
Method : other: NTP
Year : 1992
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : The information in this summary is consistent with the OECD dossier for CAS No. 81-11-8 presented at SIAM 4. The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented at SIAM 4.

According to the OECD summary, a dose of 12500 ppm corresponds to 1681 mg/kg/day in mice.

Although the summary included in the dossier for CAS No. 81-11-8 presented at SIAM 4 indicated that female mice in the 6250, 12500 and 50000 ppm dose groups had increased incidences of cystic endometrial hyperplasia, the NOEL was reported as 12500 ppm. As reported in the

study documentation, there was a significant increase in the incidence of cystic endometrial hyperplasia in females receiving the 25000 ppm dose (5/10 vs. 0/10 in control). This did not appear to be related to treatment, since the incidence did not increase with dose. Additional findings that were not reported in the SIAM 4 dossier were atrophy of ovaries and the endometrium of the uterus in high dose females and atrophy of the thymus in 5/8 high dose males. Based on these data, the NOAEL of 12500 ppm appears to have been assigned correctly.

Result : Mortality: "Six males and one female receiving 100000 ppm died during the study."

Body weight: "Mean body weight gain was significantly decreased in female mice receiving 50000 or 100000 ppm and male mice receiving 25000, 50000 or 100000 ppm."

Clinical findings: Body tremors, lethargy, emaciation and diarrhea were noted in high dose animals.

Organ weights/clinical chemistry: "There were no biologically significant changes in absolute or relative organ weights or clinical pathology results in mice."

Pathological examination: "Ulcerative inflammation of the anus and rectum was observed in mice receiving 25000 ppm and above. Female mice in the 6250, 12500 and 50000 ppm dose groups had increased incidences of cystic endometrial hyperplasia."

Test condition : Animals: Male and female B6C3F1 mice were observed for 13-15 days before use. They were 7-8 weeks old at the beginning of the studies. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 70.6 degrees F and 43.1 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Groups of 10 mice/sex received feed containing 0, 6250, 12500, 25000, 50000 or 100000 ppm test material for 13 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed twice during the 13 week study to confirm stability.

Study conduct: Animals were observed twice daily and clinical observations were recorded weekly. Animals were weighed at the beginning of the study and weekly thereafter. Food consumption was measured weekly.

At the end of 13 weeks, rats were anesthetized and blood was withdrawn from the orbital sinus plexus of all surviving animals for clinical pathology

analyses (glucose, total protein, albumin, albumin/globulin ratio, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase). Hematological analyses were not performed.

Necropsies were performed on all study animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. All animals that died or were killed prior to the end of the study, all controls, and all high dose animals received complete histopathologic examinations. These aforementioned tissues plus the adrenal gland, anus, bone and marrow (sternum), cecum, colon, duodenum, esophagus, gallbladder, ileum, jejunum, left kidney, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, prostate, rectum, salivary gland, spleen, stomach, left testis, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined in the 6250, 12500, 25000 and 50000 ppm dose groups were the anus, ovary, rectum, uterus and liver. Liver sections from all groups were stained with Oil Red O and periodic acid-Schiff (with and without diastase).

Statistical analyses: Body weight and absolute and relative (to body weight) organ weight data were analyzed using the Williams' or Dunnett's test. Clinical chemistry data were analyzed using Dunn's or Shirley's test. Incidences of pathological lesions were analyzed using the Fisher exact test. Feed consumption data were not analyzed statistically. The critical level of significance was $p <= 0.05$.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in the test diets were within the acceptable range of +/- 10% of target concentrations at both analyses.

Reliability : (2) valid with restrictions
Comparable to a guideline study with acceptable restrictions.
Hematological analyses were not performed.

Flag : Critical study for SIDS endpoint

(16)

Type : sub-acute
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 14 days
Frequency of treatm. : continuous
Post exposure period :
Doses : 0, 6250, 12500, 25000, 50000 and 100000 ppm
Control group : yes, concurrent no treatment
NOAEL : = 25000 ppm
LOAEL : = 50000 ppm
Method : other: NTP
Year : 1992
GLP : yes
Test substance : as prescribed by 1.1 – 1.4

Remark : The information in this summary is consistent with the OECD dossier for CAS No. 81-11-8 presented at SIAM 4. The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added. The NOAEL reported above is the same as the NOEL reported in the dossier presented

at SIAM 4.

According to the OECD summary, a dose of 25000 ppm corresponds to 2618 mg/kg/day in mice.

Result : "All mice survived to the end of the study. The mean body weight gains of males and females receiving 100000 ppm were significantly lower than those of the respective controls. Clinical findings included diarrhea in the mice receiving 100000 ppm. There were no chemical-related changes in absolute or relative organ weights. There were no gross or microscopic lesions related to chemical administration."

Test condition : Animals: Male and female B6C3F1 mice were observed for 16 days prior to exposure. Animals were 7-8 weeks old at study initiation. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 75.6 degrees F and 57.9 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Groups of 5 mice/sex received feed containing 0, 6250, 12500, 25000, 50000 or 100000 ppm test material for 14 days, followed by a 1 day observation period.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 5 minutes with and 10 minutes without an intensifier bar. Dose formulations were prepared weekly. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed once during the study to confirm stability.

Study conduct: Clinical observations were conducted twice daily. Animals were weighed at the start of the study, and on Days 8 and 16. Food consumption was recorded weekly. Complete necropsies were performed on all animals. The brain, heart, right kidney, liver, lungs and thymus of survivors were weighed at necropsy. All animals in the control and high dose groups received complete histopathologic examinations. Tissues examined included adrenal gland, bone and marrow (sternum), brain, colon, esophagus, gallbladder, heart, jejunum, kidney, liver, lung, mammary gland, nasal cavity, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder and uterus. Histopathology of the liver was performed on mice that received 6250, 12500, 25000 or 50000 ppm.

Statistical analyses: Data were examined using the Williams' or Dunnett's test. The critical level of significance was $p <= 0.05$.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Test material formulations were within 10% of target concentrations.

Reliability : (2) valid with restrictions
Duration of study was less than 28 days

08.07.2004 (16)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Bacterial reverse mutation assay
System of testing	:	S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration	:	100 – 5000 micrograms/plate
Cytotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 – 1.4
Test condition	:	With and without Aroclor 1254-induced male SD rat or Syrian hamster liver S9 mix
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

07.07.2004 (16)

Type	:	Cytogenetic assay
System of testing	:	Chinese Hamster CHO cells
Test concentration	:	
Cytotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 – 1.4
Test condition	:	With and without Aroclor 1254-induced male SD rat liver S9 at concentrations up to 1020 micrograms/ml or 5000 micrograms/ml
Source	:	SIAM 4 SIDS dossier for CAS No. 81-11-8
Reliability	:	(2) valid with restrictions Data came from the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

07.07.2004 (16)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

Type	:	chronic
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	103 weeks
Frequency of treatm.	:	continuous
Post exposure period	:	none

Doses	:	0, 12500, 25000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	25000 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : The information in this summary is consistent with the OECD dossier for CAS No. 81-11-8 presented at SIAM 4. The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added.

Additional information about this study is present in Section 5.4. The NOAEL listed above is for carcinogenicity. The NOAEL for repeated dose toxicity is listed in Section 5.4.

The average amount of test material ingested by males from weeks 1-13 in was 765 mg/kg/day for 12500 ppm and 1529 mg/kg/day for 25000 ppm. During weeks 14-104, the average amount of test material ingested by males was 454.5 mg/kg/day for 12500 ppm and 962.5 mg/kg/day for 25000 ppm.

The average amount of test material ingested by females from weeks 1-13 was 841 mg/kg/day for 12500 ppm and 1715 mg/kg/day for 25000 ppm. During weeks 14-104, the average amount of test material ingested by females was 528 mg/kg/day for 12500 ppm and 1085.5 mg/kg/day for 25000 ppm.

The summary in the OECD IUCLID document stated that doses of 12500 and 25000 ppm in the rats were equivalent to 558 and 1151 mg/kg day, respectively.

The marginally increased incidence of malignant pheochromocytoma in high dose male rats was not considered to be related to test material since there was no concomitant increase in the incidence of adrenal medullary hyperplasia, benign pheochromocytomas or benign or malignant pheochromocytomas combined, the incidences of malignant pheochromocytomas in the low and high dose males were within the NTP historical group range of 10-20%, and there was no clear biological distinction between adrenal medullary neoplasms diagnosed as benign or malignant.

The incidence of fibroadenomas in the controls was below the mean for NTP historical controls (39.3%) and the incidences in the dosed groups (42%) were only slightly greater than the historical controls and were within the range of historical controls (8-58%). Therefore, the increased incidences of this lesion were not considered to be related to test material.

Result : 15 month interim examination: There were no significant differences in histopathologic observations between controls and treated animals.

Pathological examination at study termination: There was a significant positive trend for malignant pheochromocytoma of the adrenal medulla in dosed males (4%, 8% and 16% in 0, 125000 and 25000 ppm groups). One malignant pheochromocytoma in a high dose male metastasized. A positive trend was not seen for benign pheochromocytomas or for benign or malignant pheochromocytomas combined. There was no corresponding dose-related increased incidence of adrenal medulllary hyperplasia (17/48, 21/50 and 13/50 in 0, 125000 and 25000 ppm groups).

The incidences of fibroadenomas in the low and high dose female rats were significantly increased relative to controls (21/50, 21/50 and 11/50, respectively).

Test condition : Animals: Male and female F344/N rats were observed for 16 days before use. They were approximately 6 weeks old at the beginning of the studies. Animals were housed 5 per cage and allowed free access to food and water. Animals were housed under 74 degrees F and 50 +/- 15.2 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Cages were rotated weekly. Five animals per sex were randomly selected and euthanized for parasite evaluation (negative) and gross observation of disease (negative). Groups of 60 rats/sex received feed containing 0, 12500, or 25000 ppm test material for 103 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed at least once every eight weeks to confirm stability.

Study conduct: Necropsies were performed on all interim (terminated at 15 weeks) and main study animals. All organs and tissues were examined for gross lesions and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all 15-month interim animals, all tissues with grossly visible lesions, all animals that died or were killed moribund prior to 21 months, and all control and high dose animals that survived to study termination. Tissues examined included the adrenal gland, bone (costochondrial junction), bone marrow (femur), brain, clitoral gland, esophagus, heart, kidney, large intestine, liver, lung, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, preputial gland, prostate, salivary gland, seminal vesicle, skin, small intestine, spleen, stomach, testis (with epididymis), thymus, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined from low dose animals that died or were killed moribund after 21 months or at study termination were gross lesions, adrenal gland, liver (males), kidney (females), mammary gland (females), pituitary gland (males) and spleen (males).

Statistical analyses: Tumor incidence data were analyzed using a logistic regression analysis which assumed that the tumors were discovered as the result of death from an unrelated cause. The Fisher exact test and the Cochran-Armitage trend test were used to analyze the overall proportion of tumor-bearing animals. Jonckheere's test was used to assess the

significance of dose-response trends.

Quality check: All slides, blocks and residual tissues were sent to the NTP Archives for inventory, slide/block match and wet-tissue audit. All neoplastic diagnoses from a randomly selected 10% of the control and high dose rats were reevaluated by a different quality assessment pathologist. The NTP Pathology Working Group chair blindly reviewed selected tissues for which there was a disagreement between the laboratory and quality assessment pathologists.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in 27/28 dose formulations were within the acceptable range of +/- 10% of target concentrations at both analyses. The sample that was not within this range was remixed.

Conclusion : "There were no chemical-related increased incidences of neoplasms at any site in rats."

Reliability : (1) valid without restriction
Comparable to a guideline study

(16)

Species : rat
Sex : male/female
Strain : other
Route of admin. : oral feed
Exposure period : 103 weeks
Frequency of treatm. : daily
Post exposure period :
Doses : 0, 40, 200 and 100 ppm
Result :
Control group : yes, concurrent no treatment
Method :
Year : 1975
GLP : no data
Test substance :

Remark : In an investigation of the anti-tumor activities of stilbene derivatives used as brighteners, a marked tumor-inhibiting activity on solid forms of Ehrlic carcinoma, sarcoma 180 and carcinoma 63 was detected. Stilbene derivatives showed no effects on Ehrlich ascites carcinoma.
It is not known if the salt or free acid (CAS No. 81-11-8) was tested.

Source : 3V Sigma S.p.A. Mozzo Bergamo
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (14)

Type :
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 2 years
Frequency of treatm. : daily (feeding study)
Post exposure period : no
Doses : 0, 6250 or 12500 ppm
Control group : yes

NOAEL		12500 ppm
Method	:	other: NTP
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : The information in this summary is consistent with the OECD dossier for CAS No. 81-11-8 presented at SIAM 4. The summary presented at SIAM 4 has been edited to be in conformance with new guidelines. The results for different species and different times of treatment are now presented in separate summaries. Information from the OECD summaries is presented within quotation marks. Additional information has been added.

Additional information about this study is present in Section 5.4. The NOAEL listed above is for carcinogenicity. The NOAEL for repeated dose toxicity is listed in Section 5.4.

The average amount of test material ingested by males from weeks 1-13 was 836 mg/kg/day for 6250 ppm and 1738 mg/kg/day for 12500 ppm. During weeks 14-104, the average amount of test material ingested by males was 763 mg/kg/day for 6250 ppm and 1565 mg/kg/day for 12500 ppm.

The average amount of test material ingested by females from weeks 1-13 was 997 mg/kg/day for 6250 ppm and 2081 mg/kg/day for 12500 ppm. During weeks 14-104, the average amount of test material ingested by females was 666 mg/kg/day for 6250 ppm and 1444 mg/kg/day for 12500 ppm.

The summary in the OECD IUCLID document stated that doses of 6250 and 12500 ppm in the mice were equivalent to 776 and 1656 mg/kg day, respectively.

Result : "There were no chemical-related increased incidences of neoplasms at any site in mice."

Test condition : Animals: Male and female B6C3F1 mice were observed for 13 days before use. They were approximately 6 weeks old at the beginning of the studies. Animals were housed 5 per cage initially and allowed free access to food and water. Male mice were housed individually from weeks 39 to termination. Animals were housed under 74 degrees F and 50 +/- 15.2 % average temperature and humidity, respectively. They were kept under a 12 hour light/12 hour dark light cycle. There were 6-12 room air changes per hour. Cages were rotated weekly. Five animals per sex were randomly selected and euthanized for parasite evaluation (negative) and gross observation of disease (negative). Groups of 60 mice/sex received feed containing 0, 6250, or 12500 ppm test material for 103 weeks.

Test material formulation: Test material was stored in the dark, under refrigeration. A premix with test material and feed was prepared using a mortar and pestle. The premix and rest of the feed were layered into a Patterson-Kelly twin-shell blender and mixed for 20 minutes with an intensifier bar. Dose formulations were prepared every two weeks. The homogeneity of the diet was tested by extracting feed with a buffered solution of methanol (pH 10.0 +/- 0.1), spinning the mixture in a centrifuge, and further diluting the extract with methanol. The absorbance of the samples was measured at 342 nm. For the stability studies, feed samples were extracted with the same solution used in the homogeneity analysis. The extracts were mixed with methanol and spun in a centrifuge. An aliquot of the supernatant was injected into an HPLC system equipped with a uBondapak C18 column and a 340 nm detector. The mobile phase was 0.005 M tetrabutylammonium hydroxide in methanol (adjusted to pH 7.4 with phosphoric acid) and 0.005 M tetrabutylammonium hydroxide in water (with the same amount of phosphoric acid used to adjust the pH of the

methanol solution. The ratio of the two solvents was 14:86 and the flow rate was 1.5 ml/min. Dose formulations were analyzed at least once every eight weeks to confirm stability.

Study conduct: Necropsies were performed on all interim (15 week termination) and main study animals. All organs and tissues were examined for gross lesions and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all 15-month interim animals, all tissues with grossly visible lesions, all animals that died or were killed moribund prior to 21 months, and all control and high dose animals that survived to study termination. Tissues examined included the adrenal gland, bone (costochondrial junction), bone marrow (femur), brain, esophagus, gallbladder, heart, kidney, large intestine, liver, lung, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid, pituitary gland, prostate, salivary gland, seminal vesicle, skin, small intestine, spleen, stomach, testis (with epididymis), thymus, thyroid gland, trachea, urinary bladder, and uterus were fixed and examined microscopically. Tissues examined from low dose animals that died or were killed moribund after 21 months or at study termination were gross lesions, liver (males) and lung.

Statistical analyses: Tumor incidence data were analyzed using a logistic regression analysis which assumed that the tumors were discovered as the result of death from an unrelated cause. The Fisher exact test and the Cochran-Armitage trend test were used to analyze the overall proportion of tumor-bearing animals. Jonckheere's test was used to assess the significance of dose-response trends.

Quality check: All slides, blocks and residual tissues were sent to the NTP Archives for inventory, slide/block match and wet-tissue audit. All neoplastic diagnoses from a randomly selected 10% of the control and high dose rats were reevaluated by a different quality assessment pathologist. The NTP Pathology Working Group chair blindly reviewed selected tissues for which there was a disagreement between the laboratory and quality assessment pathologists.

Test substance : Purity of the test material was 76%. Impurities were water (approximately 14%), sodium chloride (approximately 6%), and 4,4' -ethylene-2-dianaline sulfonic acid (approximately 4%). Stability studies indicated that when stored protected from light, the bulk chemical was stable for 2 weeks at temperatures up to 60 degrees C. Concentrations of material in 27/28 dose formulations were within the acceptable range of +/- 10% of target concentrations at both analyses. The sample that was not within this range was remixed.

Reliability : (1) valid without restriction
Comparable to a guideline study

(16)

5.8.1 TOXICITY TO FERTILITY

Remark : This material has not been tested for reproductive toxicity. Endpoint filled by category approach. Refer to the dossier for CAS No. 81-118 for data to fill this endpoint.

07.07.2004

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Remark : This material has not been tested for developmental toxicity. Endpoint filled by category approach. Refer to the dossier for CAS No. 81-11-8 for data to fill this endpoint.

07.07.2004

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : other

Result : In vitro studies:
DES and E2 exhibited characteristic binding affinities for the estrogen receptor. The EC50 value for displacement of 3H-E2 was 3.33 x 10E-9 M for DES and 1.33 x 10E-8 M for E2. In contrast, CAS No. 7336-20-1 was ineffective in displacing bound E2, even at concentrations approaching its solubility limit (10E-4 M).
In vivo studies:
Subcutaneous injections of DES at doses of 25 or 85 micrograms/kg bw resulted in marked, gross changes in uterine tissue characteristic of estrogenic activity. Gravimetric measurements of uteri from DES-treated rats demonstrated increases up to 644% of control values in nonblotted tissues and 420% of control in blotted tissues ($p < 0.01$). CAS No. 7336-20-1 had no effect on uterine appearance or weight at either of the doses. Spleen and kidney weights were not affected by treatment.

Test condition : In vitro studies:

Competitive binding assays were conducted using cytosolic preparations from MCF-7 cells, a human breast cell cancer line. Cells (5 x 10E7) were suspended in medium and homogenized until they were more than 90% disrupted as observed by phase microscopy. Homogenates were spun in a centrifuge (105,000 g) and the supernatant was used immediately. Cytosolic extracts (100 microliters) were incubated with various concentrations of unlabeled CAS No. 7336-20-1, diethylstilbestrol (DES), or 17beta-estradiol (E2) along with 10 nM 3H-E2 (97.1 Ci/mmol) for 20 hrs at 4 degrees C. The binding reaction was terminated by adding dextran-coated charcoal and further incubating the mixture for 15 min at 4 degrees C. This mixture was pelleted by centrifugation and the resulting supernatants were mixed with 5.0 ml of scintillation cocktail. Radioactivity was quantified using scintillation counting in a Beckman LS 6000 IC.

In vivo studies:
Uterotropic effects of DES and CAS No. 7336-20-1 were evaluated in immature, female Sprague Dawley rats. Groups of 5 rats (18-19 days old) were treated once daily for 3 consecutive days by s.c. injection with 25 or 85 micrograms/kg bw DES or 230 or 750 mg/kg bw CAS No. 7337-20-1. Dosing solutions were made up in 0.1 to 0.3 ml of sunflower oil containing 10% ethanol immediately before use, and special precautions were taken to protect CAS No. 7336-20-1 from light. The highest dose of CAS No. 7336-20-1 give was the highest achievable dose in the chosen vehicle. Approximately 24 hrs after the last injection, animals were euthanized and

uteri were excised. Uterine weights were recorded before and after draining of luminal fluid. Spleen and kidney weights also were recorded.

Statistical analyses:
Homogeneity of organ weight data was confirmed by Bartlett's test. When subsequent analyses of variance revealed significant differences in group means, Duncan's multiple range test was used to determine if organ weights in treated animals were different from controls. The critical values for significance were $p < 0.05$ and $p < 0.01$.

Test substance : CAS No. 7336-20-1, 99.6% pure

Reliability : (4) not assignable
The study was not available for review. Information came from an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

08.07.2004 (10)

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

(1) BASF AG data (no additional information)

(2) Bayer AG (no year listed). Unpublished data.

(3) Bayer AG (1986). Unpublished data from a laboratory notebook, dated 03.07.1986.

(4) Bayer AG (1986). Unpublished data from a laboratory notebook, dated 19.06.1986.

(5) Bayer AG (1991). Calculation UWS-Produktsicherheit

(6) Bayer AG (1993). Report No. 22194, April 19, 1993

(7) Ciba-Geigy AG (1986). Unpublished data, April 1986.

(8) Ciba-Geigy AG (2005). Unpublished data.

(9) ETAD. 1992. Ecological properties of aromatic aminosulfonic acids. Internal Research Project 3018 (unpublished study). May, 1992.

(10) Hostetler KA et al. (1996). J. Toxicol. Environ. Health **48**, 141-149

(11) Krotlinger F (1993). 4,4'-Diaminostilben-2,2'-disulfonsaure Di-Na-Salt ft./Flavonsaure S. Study for skin and eye irritation/corrosion in rabbits. Bayer AG, Fachbereich Toxikologie Study No. T6041047, dated 18.5.1992 (unpublished study).

(12) Loeser E (1979). Bayer AG data, short report, 3. 5. 1979

(13) RTECS: NIOSH USA, WJ 6603000 (no additional information)

(14) Saito C. Antitumor activities of fluorescent whitening agents of the stilbene class. Oyo Yakuri, 4,521-524 (no year listed).

(15) Sörensen M and Frimmel FH (1996). Photochemical degradation of hydrophillic xenobiotics in the UV/H2O-process. Influence of bicarbonate on the degradation rate of EDTA, 2-amino-1-naphthalenesulfonate, diphenyl-4-sulfonate, and 4,4'-diaminostilbene-2,2'-disulfonate. Acta Hydrochimica et Hydrobiologica, **24,** 185-188.

(16) U.S. Dept of Health and Human Services (1992). Toxicology and carcinogenesis studies of 4,4'-diamino-2,2'stilbene disulfonic acid, disodium salt (CAS No. 7336-20-1) in F344/N rats and B6C3F1 mice. Technical Report Series 412, NIH publication No. 92-3143, dated August, 1992.

(17) Thyssen J (1979). Bayer AG data, short report, 6. 8. 1979

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

201-16114

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IUCLID

Data Set

Existing Chemical	:	ID: 3709-43-1
CAS No.	:	3709-43-1
EINECS Name	:	disodium 4,4'-dinitrostilbene-2,2'-disulphonate
EC No.	:	223-051-2
TSCA Name	:	Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis[5-nitro-, disodium salt
Molecular Formula	:	C14H10N2O10S2.2Na

Producer related part

Company	:	PCA Services, Inc
Creation date	:	22.07.2004

Substance related part

Company	:	PCA Services, Inc
Creation date	:	22.07.2004
Status	:	
Memo	:	
Printing date	:	21.08.2005
Revision date	:	21.08.2005
Date of last update	:	21.08.2005
Number of pages	:	23
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	
Name	:	CHEMAG Aktiengesellschaft
Contact person	:	
Date	:	
Street	:	
Town	:	60325 Frankfurt
Country	:	Germany
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type	:	
Name	:	CIBA SPECIALTY CHEMICALS PLC
Contact person	:	
Date	:	
Street	:	ASHTON NEW ROAD
Town	:	M11 4AP MANCHESTER
Country	:	United Kingdom
Phone	:	0161 223 1391
Telefax	:	0161 223 4315
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type	:	
Name	:	Clariant Productos S.A.
Contact person	:	
Date	:	
Street	:	Poligano Industrial Pratense C
Town	:	08820 El Prat de LLOBREGATT
Country	:	Spain
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type	:	
Name	:	Hickson & Welch Ltd.
Contact person	:	
Date	:	
Street	:	Wheldon Road
Town	:	WF10 2JT Castleford
Country	:	United Kingdom
Phone	:	
Telefax	:	

Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Type	:	
Name	:	Hickson and Welch Ltd
Contact person	:	
Date	:	
Street	:	Wheldon Road
Town	:	WF102JT Castleford
Country	:	United Kingdom
Phone	:	0977 556565
Telefax	:	0977 518058
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	
Substance type	:	organic
Physical status	:	solid
Purity	:	
Colour	:	
Odour	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

4,4'-Dinitrostilbene-2,2'-disulphonic acid, disodium salt

Source	:	Hickson & Welch Ltd. Castleford Hickson and Welch Ltd Castleford EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

DNS

Source : Hickson & Welch Ltd. Castleford
Hickson and Welch Ltd Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 10000 - 50000 tonnes

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000.

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Remark : All data in this section were reproduced from an IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000. No reliability ratings were assigned.

Type of use : type
Category : Non dispersive use

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : type
Category : Wide dispersive use

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : industrial
Category : Chemical industry: used in synthesis

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use : industrial
Category : Textile processing industry

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type of use	:	use
Category	:	Colouring agents
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Type of use	:	use
Category	:	Intermediates
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Remark	:	Submitter is not aware of any assigned occupational exposure limit value.
Source	:	Hickson & Welch Ltd. Castleford Hickson and Welch Ltd Castleford EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000.

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by	:	other: Selbsteinstufung (Translated as “Self-classification”)
Labelled by	:	
Class of danger	:	1 (weakly water polluting)
Source	:	CHEMAG Aktiengesellschaft Frankfurt EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000.

(1)

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation	:	Stoerfallverordnung (DE) (Translated as “Self-classification”)
Substance listed	:	no
No. in Seveso directive	:	
Source	:	CHEMAG Aktiengesellschaft Frankfurt EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000.

(1)

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by :
Number : 3.1.3 (total dust)
Class of danger :

Source : CHEMAG Aktiengesellschaft Frankfurt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000.

(1)

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : In the workplace the substance may be absorbed by inhalation of dust or by ingestion. It is not believed that absorption through intact skin is significant. Substance is handled as a wet cake and dry powder. Basic atmospheric monitoring indicates dust levels <10 mg/m3 (8hr TWA). Main release will be to aquatic environment as a result of water solubility.

Substance is produced by air oxidation of 4-nitrotoluene-2-sulphonic acid in aqueous solution.

Substance is principally used on site by the submitter to produce DAS (81-11-8) and small amounts are sold to producers of colouring agents.

Source : Hickson & Welch Ltd. Castleford
Hickson and Welch Ltd Castleford
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable
Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000.

1.11 ADDITIONAL REMARKS

Remark	:	Substance is not classified as dangerous according to International transport regulations. Substance is despached from our works in fibre kegs of ca 75 kg.
Source	:	Hickson & Welch Ltd. Castleford Hickson and Welch Ltd Castleford EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000.

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value		349.84 °C
Decomposition		
Method		other: calculation using EPIWIN MPBPWIN (v1.41)
Year		2005
GLP		no
Test substance		as prescribed by 1.1 - 1.4
Remark	:	Since the substance is a salt, it will have a melting point above 300 degrees C, as is consistent with other members of the category.
Test condition	:	CAS No 3709-43-1 was inputted to model.
Reliability	:	(2) valid with restrictions Data were obtained by model estimation.
Flag	:	Critical study for SIDS endpoint

2.2 BOILING POINT

Remark	:	No data available. Since the substance is a salt, a boiling point is irrelevant for this material.

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Remark	:	No data available. Since the substance is a salt, and does not exist as a neutral molecule, it cannot exist in vapor form or exert a meaningful vapor pressure.

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	-2.52
pH value	:	
Method	:	other: calculated using EPIWIN KOWWIN (v1.67) Model, inputting CAS No. 3709-43-1
Year	:	2005
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Reliability	:	(2) valid with restrictions. Value was obtained by modeling.
Flag	:	Critical study for endpoint

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	water
Value	:	No data available. Endpoint filled by category approach. Refer to the dossier for CAS No. 78447-91-3 for data to fill this endpoint.

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Remark	:	This material does not volatilize to any degree, since it is an ionized, organic salt. Therefore, it will not be found in any significant concentration in the atmosphere other than in particle form. For this reason, atmospheric photodegradation is not a relevent degradative pathway.
Reliability	:	(2) valid with restrictions. Information is based on chemical structure.

3.1.2 STABILITY IN WATER

Remark	:	No data available. The substance does not contain any functional groups subject to hydrolysis, and should be stable in water.

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other: air, water, soil, biota
Air	:	1.04 E-18 % (Fugacity Model Level III)
Water	:	59.1 % (Fugacity Model Level III)
Soil	:	% (Fugacity Model Level I)
Biota	:	.112 % (Fugacity Model Level II/III)
Soil	:	40.8 % (Fugacity Model Level II/III)
Method	:	other: calculation using EPIWIN v3.11
Year	:	2005
Result	:	Half-lives in various media are air:1.47 hours; water: 1440 hours; soil: 1440 hours; and sediment: 5760 hours. The Henry's Law Constant [calculated by EPIWIN HENRY (v3.10)] is 4.24 E-22 atm-m3/mol (bond est.). The soil-sediment coefficient [calculated by EPIWIN PCKOC (v1.66)] is Koc = 1.47.E+4.
Test condition	:	Inputs to the model are CAS No. 3709-43-1 and emission rates: air: 0 kg/hr, water: 1000 kg/hr, and soil: 1000 kg/hr.
Reliability	:	(2) valid with restrictions Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	

Concentration	:	84.03 mg/l related to Test substance related to
Contact time	:	31 day(s)
Degradation	:	= 4.3 (±) % after 31 day(s)
Result	:	under test conditions no biodegradation observed
Kinetic of testsubst.	:	10 day(s) = 0 % 21 day(s) = 1 % 31 day(s) = 4.3 % % %
Deg. product	:	
Method	:	other:Modified OECD-Confirmatory Test (OECD 2) A-12
Year	:	1986
GLP	:	no data
Test substance	:	other TS: FAT 90159/A
Remark	:	The study was in German and was translated to English. The concentration of the inoculum and whether it was acclimated were not stated. There was no mention of a positive control.
Test condition	:	TOC content of test substance: 23.8% (Method A-13) TOC content of test substance: 25.3% (elemental analysis) TOC content of the nutrient solution: 107.3 mg/l
Test substance	:	Documents supplied by the manufacturer indicate that the material contained 60% CAS No. 3709-43-1 and 35% water. The remaining 5% was uncharacterized.
Reliability	:	(2) valid with restrictions Basic data given.

26.07.2004 (2)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Remark	:	The study described below is insufficient for assessment. Endpoint filled using category approach. Refer to the dossiers for CAS Nos. 81-11-8, 7336-20-1 and 78447-91-3.
Type	:	
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	>= 1000
LC50	:	>= 1000
LC100	:	>= 1000
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	other TS
Remark	:	The study was in German and was translated to English.
Test substance	:	Documents supplied by the manufacturer indicate that the material contained 60% CAS No. 3709-43-1 and 35% water. The remaining 5% was uncharacterized.
Reliability	:	(4) not assignable Insufficient documentation.

(2)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Remark	:	No data available. Endpoint filled using category approach. Refer to the dossiers for CAS Nos. 81-11-8 and 7336-20-1.

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Remark	:	No data available. Endpoint filled using category approach. Refer to the dossiers for CAS Nos. 81-11-8 and 7336-20-1.

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Remark	:	The study described below is insufficient for assessment. Endpoint filled using category approach. Refer to the dossiers for CAS Nos. 81-11-8, 7336-20-1 and 78447-91-3.
Type	:	LD50
Value	:	> 16000 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Hickson and Welch Ltd Castleford EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable Primary reference was not available. Data were reproduced from an IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000.

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	.5 g
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	3
Vehicle	:	water
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1986
GLP	:	no data
Test substance	:	other TS: FAT 90159/A
Result	:	All scores were 0 (no edema or erythema). The animals gained weight over

the course of the study.

Test condition : Three male New Zealand white rabbits (2290-2560 g, approximately 12-14 weeks old) were acclimated for 5 days before use. The animals were housed individually, and kept at 20 +/- 3 degrees C and 30-70% relative humidity under a 12-hour light/dark cycle. They received standard pelletized diet and fresh water ad libitum.

An area of at least 6 cm2 was shaved on both flanks of the animals approximately 24 hours before treatment. Test material (0.5 g) was applied to a gauze patch (20 cm2), which was placed in contact with one of the flanks. A control patch was applied to the contralateral flank. Both gauze patches were moistened before application with distilled water. The patches were loosely covered with aluminum foil (36 cm2) and held in place for 4 hours by adhesive tape. The animals were checked daily for mortality and symptoms of systemic toxicity. Body weights were recorded at the beginning of the study and on day 3.

The patches were removed after 4 hours and skin reactions were evaluated 1, 24, 48 and 72 hours after patch removal. Erythema/eschar and edema were both scored on a scale of 0-4, according to OECD Guideline 404. The irritant/corrosive potency of the material was classified according to the EEC commission directive No. 83/467/1983.

Test substance : Documents supplied by the manufacturer indicate that the material contained 60% CAS No. 3709-43-1 and 35% water. The remaining 5% was uncharacterized.

Reliability : (1) valid without restriction
Guideline study.

(3)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	3
Vehicle	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1986
GLP	:	no data
Test substance	:	other TS: FAT 90159/A

Result : Conjunctival redness scores of 1 (some blood vessels definitely hyperaemic) were observed up to 72 hours in one rabbit. In another rabbit, conjunctival scores of 2 (diffuse, crimson color, with individual vessels not easily discernable) were observed after 1 and 24 hours, and a score of 1 was observed at 48 hours. In the third rabbit, the conjunctival score at 1 hour was 2, followed by 1 at 24, 48 and 72 hours. Chemosis scores of 1 (any swelling above normal, including nictitating membrane) were observed at 1 and 24 hours in 2 animals and at 1 hour in the third animal. All other scores were 0. The average scores for redness over the 24-72 period were 1 in all of the animals. The average scores for chemosis over the 24-72 period were 0.33, 0.33 and 0 in the three animals.

According to the EC classification, the results from 24 to 72 hours were classified as non-irritant (redness and chemosis scores >= 2.5 or 2, respectively were not obtained). The eye reactions were reversible until

the end of the observation period on day 7.

Slight weight loss was observed in two of the animals on day 3. Weights of all the animals on day 7 were greater than initial weights.

Test condition : Three male New Zealand white rabbits (2590-2720 g, approximately 12-14 weeks old) were acclimated for 5 days before use. The animals were housed individually, and kept at 20 +/- 3 degrees C and 30-70% relative humidity under a 12-hour light/dark cycle. They received standard pelletized diet and fresh water ad libitum.

Test material (0.1 ml) was placed into the conjunctival sacs of the right eye of each animal after gently pulling away the lower lid from the eyeball. The lids were then held together for about one second. The left eye remained untreated and served as a control. The treated eye was not washed. The animals were checked daily for mortality and symptoms of toxicity. The animals were weighed at the start of the study and on days 3 and 7.

Ocular reactions were evaluated 1, 24, 48 and 72 hours after the instillation of test material according to the OECD scoring system. Because reactions were observed at 72 hours, the observation period was extended to 7 days. A slit-lamp was used to facilitate the evaluation. The irritant/corrosive potency was classified according to the EEC commission directive No. 83/467, 1983.

Test substance : Documents supplied by the manufacturer indicate that the material contains 60% CAS No. 3709-43-1 and 35% water. The remaining 5% was uncharacterized.

Reliability : (1) valid without restriction
Guideline study.

(4)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Remark : No data available. Endpoint filled using category approach. Refer to the dossiers for CAS No 7336-20-1.

5.5 GENETIC TOXICITY 'IN VITRO'

Remark : The studies described below are insufficient for assessment. Endpoint filled using category approach. Refer to the dossiers for CAS Nos. 81-11-8, 7336-20-1 and 78447-91-3 for data to fill the mutagenicity endpoint and the dossiers for CAS Nos. 81-11-8 and 7336-20-1 for data to fill the chromosomal aberrations endpoint.

Type : Ames test
System of testing : S. typhimurium TA100
Test concentration :
Cytotoxic concentr. :
Metabolic activation : with
Result :
Method :
Year : 1978
GLP :
Test substance : other TS: 4,4'-Dinitro-2,2'-stilbenedisulfonic acid

Remark : The study documentation was in German and was translated to English by the summary preparer.

Result : The material showed a weak increase in mutations at 30 micrograms/plate.

There was no apparent effect at 60 micrograms/plate. The result with the other concentration was not listed. A dose/response relationship was detected at the level of $p < 0.05$, but not at $p < 0.01$ (the criterion for a significant effect). Therefore, the study was negative.

Test condition : Agar plates containing the bacteria (numbers were not listed) were incubated for 48 hours together with S-9 from phenobarbital –induced mouse liver (2 mg protein), test material (3 concentrations) and the required co-factors. Three to five replicates were plated per concentration. The three concentrations tested were not stated. The criterion for the acceptance of mutagenic effects was the observation of a dose effect relationship at a level of $p < 0.01$. The level of significance was calculated with the aid of a distribution free range variance analysis according to Jonkheere.

Test substance : The material was technical grade, with no chemical analysis.

Reliability : (4) not assignable
Documentation insufficient for assessment. The study was not performed without metabolic activation. Doses used and results at each dose were not tabulated. It is unknown if cytotoxicity occurred at the concentration causing a positive response. The study should have been repeated.

(5)

Type : Ames test
System of testing : E. coli
Test concentration :
Cytotoxic concentr. :
Metabolic activation : with
Result : ambiguous
Method :
Year : 1978
GLP :
Test substance : other TS: 4,4'-Dinitro-2,2'-stilbenedisulfonic acid

Remark : The study documentation was in German and was translated to English by the summary preparer. Whereas the results section states that strain WP2uvrA- was used, a table indicates that strain K12 (343/113)arg56 was used. There is no mention of a dose response relationship in the text, but an accompanying table indicated that a questionable dose response relationship occurred.

Result : The material showed a “weak” increase in mutations at 60 micrograms/plate. It is not known if the increase was at the $p < 0.05$ or $p < 0.1$ level. Results at other concentrations were not listed.

Test condition : Agar plates containing the bacteria (numbers were not listed) were incubated for 48 hours together with S-9 from phenobarbital –induced mouse liver (2 mg protein), test material (three concentrations) and the required co-factors. Three to five replicates were plated per concentration. The three concentrations tested were not stated. The criterion for the acceptance of mutagenic effects was the observation of a dose effect relationship at a level of $p < 0.01$. The level of significance was calculated with the aid of a distribution free range variance analysis according to Jonkheere.

Test substance : The material was technical grade, with no chemical analysis.

Reliability : (4) not assignable
Documentation insufficient for assessment. The strain used is unknown. A study without metabolic activation was not performed. Doses used and results at each dose were not tabulated. It is unknown if cytotoxicity occurred at the concentration causing a positive response. The study should have been repeated.

(5)

5.6 GENETIC TOXICITY ‘IN VIVO‘

Remark : No data available.

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Remark : No data available. Endpoint filled using category approach. Refer to the dossiers for CAS Nos. 81-11-8 and 7336-20-1 for data to fill this endpoint.

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Remark : No data available. Endpoint filled using category approach. Refer to the dossier for CAS No. 81-11-8.

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

(1) CHEMAG AG (1995). Sicherheitsdatenblatt 4,4'-Dinitrostilbene-2,2'-disulfonsäure, 02.10.1995

(2) Ciba-Geigy (1986). Biodegradative elimination, acute fish toxicity and bacterial sludge toxicity. Fat No. 90159A. Division of Dyes and Chemicals Research and Development, Series 367, Run Number 3938 (unpublished study).

(3) Ciba-Geigy Limited (1986). Final Report. FAT 90159/A. Acute dermal irritation/corrosion study in the rabbit. Experimental Toxicology GU 2.1, Project Number 851038, dated February 27, 1986 (unpublished study).

(4) Ciba-Geigy Limited (1986). Final Report. FAT 90159/A. Acute eye irritation/corrosion study in the rabbit. Experimental Toxicology GU 2.1, Project Number 851037, dated February 26, 1986 (unpublished study).

(5) Norpoth K (1977). Report of the examination of eleven different compounds for their mutagenic potency in the oxygenase-enterobacteriacea test system, Report for Bayer AG, dated 22.7.1977 (unpublished study).

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT